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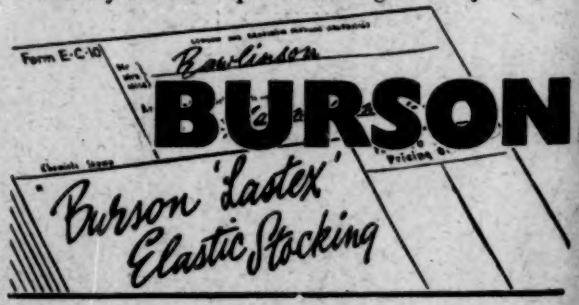

BRITISH MEDICAL JOURNAL

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LIVING MODIFIED VIRUSES AS IMMUNIZING AGENTS*

BY

HERALD R. COX, Sc.D.

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(From Viral and Rickettsial Research, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York)

Every medical investigator of the twentieth century counts among his scientific forebears the two great Germans Paul Ehrlich and Emil von Behring. Born a day apart, friends and co-workers, both Nobel Prize winners, appropriately they have been called "twin sons of science and humanity." I leave to others the enumeration of their many accomplishments.

One writer has said that Behring forged the sword of serotherapy, but Ehrlich ground its edge. On this occasion, no one can speak of the weapons against disease we are now creating without first acknowledging the power of those fashioned by Ehrlich and von Behring.

Jenner and Pasteur

The purpose of this paper is to review a mighty weapon we now possess—namely, living modified viruses as immunizing vaccines. Unquestionably, Jenner's use of cowpox or vaccinia virus on a large scale to protect against smallpox was the first instance of immunization with a living, attenuated virus. It had been recognized for many years in England, France, and Germany that milkmaids who had contracted cowpox were spared during ravaging epidemics of smallpox. The observation of this fact was not original with Jenner. The merit of his work rests upon the fact that he started out with the hope of making his conception a permanent working principle in science, based upon experimental demonstration, and he succeeded.[1] In short, Jenner transformed a rural tradition into a living prophylactic principle. Popular aversion to vaccination was overcome, and the practice spread rapidly in Europe and America. The effect of Jenner's work is apparent in the rapid advances serotherapy and immunology have made, and in the results of compulsory vaccination in Germany and Holland, where the mortality curve of smallpox approaches zero. Striking, indeed, was the relative immunity of the German army during the Franco-Prussian War in 1870–1, in which the unvaccinated French prisoners lost 1,963 out of 14,178 cases of smallpox, whereas the Germans, who had been revaccinated within two years' time, had 4,835 cases with only 278 deaths.[2]

We are indebted to Pasteur, who, in his studies on fowl cholera, first recognized the importance of microbic variation for practical purposes of medical use.[3] His discovery of preventive inoculation with attenuated living agents resulted from an accident. During a vacation period, virulent cultures of the chicken cholera organism left in the laboratory became avirulent, but were found to act as preventive vaccines when inoculated birds were later challenged by injections of living, fully virulent material. The attenuated culture could be passed through several successive generations and still retain its immunizing property. Pasteur later studied the agents of anthrax, swine measles (*rouget des porcs*), and rabies, and established the important principle that the invasive and pathogenic properties of a virus can be altered by successive passages through appropriate hosts. This work gave rise to one of the most illuminating ideas in the history of medical science: that the origin or extinction of an infectious disease may be simply the result of the enhancing or attenuation of its virus by external conditions. Pasteur applied the principle of passing the virus serially in an unnatural host to develop a rabbit-adapted, fixed rabies virus which was used as a living vaccine.

Viral Agents

The basic investigations of Jenner and Pasteur have been gradually extended during the intervening years so that to-day there are at least 13 different viral agents being used as living attenuated vaccines in the practice of human or veterinary medicine. These are: African horse-sickness, blue-tongue, canine distemper, fowl-pox, hog cholera, infectious bronchitis, laryngotracheitis, Newcastle disease, pigeon-pox, rabies, rinderpest, vaccinia, and yellow fever.[4] Three of these—rabies, vaccinia, and yellow fever—are used extensively for the immunization of man. The remainder, plus rabies, are used widely in the field of veterinary medicine. It is interesting to note that fowl-pox, infectious bronchitis, laryngotracheitis, Newcastle disease, pigeon-pox, and vaccinia are viral strains of relatively low pathogenicity recovered directly from their natural hosts (Table I).

TABLE I.—*Modified Living Vaccines Derived from Natural Hosts*

Disease	Natural Host	Vaccine Source
Fowl-pox	Chicken	Chick embryo
Infectious bronchitis	"	" "
Laryngotracheitis	"	" "
Newcastle disease	"	" "
Pigeon-pox	Pigeon	" "
Smallpox	Man	Calf

*Presented at Frankfurt-on-Main, Germany, March 16, 1954, on the occasion of the 100th anniversary of the birthdays of Paul Ehrlich and Emil von Behring.

Seven of the immunizing agents—African horse-sickness, blue-tongue, canine distemper, hog cholera, rabies, rinderpest, and yellow fever—are laboratory-induced or man-made mutants (Table II).

TABLE II.—*Laboratory-induced Modified Living Vaccines*

Disease	Natural Host	Vaccine Source
African horse-sickness	Horse	Mouse brain
Blue-tongue	Sheep	Chick embryo
Canine distemper	Dog, ferret, mink	,, ,,
Hog cholera	Swine	Rabbit
Rabies	Man, dog, cattle, etc.	Rabbit, chick embryo
Rinderpest	Cattle, buffalo	Goat, rabbit, chick embryo
Yellow fever	Man	Chick embryo, mouse brain

Apart from the above, there are several other viruses which have been used at one time or another on an experimental scale for the immunization of man or animals.[4] Some of these are: Colorado tick fever,[5] dengue fever,[6] infectious hepatitis,[7] influenza,[8 9 10] mumps,[11 12] poliomyelitis,[13 14] and Rift Valley fever.[15]

Properties Required of a Good Vaccine

I believe that all those who have had sufficient experience will agree that the greatest success in immunizing against viral infections has been achieved by the use of living mutants lacking the invasiveness and pathogenicity of the parent strain, but retaining the same antigenic structure. In practically all cases, the immunity induced by living attenuated vaccines is of higher degree and longer duration than that produced by inactivated viral preparations. To demonstrate, I mention the successful use of vaccinia virus and yellow-fever vaccine in protecting man; and the durable results obtained with the Flury strain rabies vaccine in dogs; the rabbit-adapted hog cholera virus in swine; and the quadrivalent blue-tongue vaccine in sheep. Each of these preparations has been extensively used and has passed the test of time with flying colours.

Certain specifications must be met in order to secure a practical and reliable vaccine that can be widely used with confidence.

(1) The vaccine—when applied by the proper manner and route—must be safe for general use. It must not induce a severe or fatal infection in the host it is intended to immunize.

(2) The vaccine must be attenuated to such a degree that it will not only be innocuous for the host but will have such low virulence or "spreading" potential that it cannot be transmitted readily from one susceptible host to another, thereby conceivably regaining its original invasiveness and virulence.

(3) The product must be adequately tested and known to be free at all times of any other viral, rickettsial, or bacterial contaminant that could be considered, even remotely, as potentially pathogenic.

(4) The product must contain enough antigen to bring about an adequate immunizing infection under all types of field conditions. We know that to be effective as an antigen an attenuated live virus must multiply in the tissues of the host. For this to take place a sufficient number of living virus particles must be present in the inoculum. The optimal range of virus content must be quantitatively controlled and accurately determined individually for every lot of vaccine produced.

(5) The product must be rigidly controlled not only quantitatively but in a biologically qualitative manner as well, to ensure that the infectious agent has enough invasiveness to establish and guarantee immunity. Thus, the infectious agent must be sufficiently attenuated to render it safe for use, but not overattenuated to the point that it ceases to be a good immunogenic antigen.

(6) The product must be stable, so that it will retain its immunogenic capacity unimpaired under all types of adverse conditions such as light, moisture, temperature, and travel (shipping conditions) for long periods of time.

(7) The product must be produced by a practical method, so that it will not be too expensive, but can be afforded by all who need it.

The above are the specifications which research scientists and production workers must meet for a marketable vaccine worthy of a good reputation. As might be surmised, there is no ready formula available at present for making viral vaccines by a mould or template system. Every vaccine now available has come about only after many devoted workers have put in long years of painstaking and often heart-breaking toil.

It seems to me of interest to describe briefly a few viral agents commonly employed to-day as living attenuated vaccines.

Yellow Fever

I believe we can safely say that yellow fever vaccine represents the most successful attenuated living viral immunizing agent so far "hand tailored" in the laboratory for use in man. Two strains are used currently for human vaccination: the French neurotropic (mouse brain) and the 17D (chick embryo). Both types of vaccine are based on the original finding of Theiler[16 17] that white mice, if inoculated intracerebrally, are susceptible to yellow fever, and that a fixed virus for mice, with a shortened incubation period and heightened virulence, can be produced by repeated passage through these animals. The original French strain of yellow fever virus was isolated from a Syrian in Dakar in 1929[17] and was adapted to mice by Theiler in 1930.[18] It lost its capacity to produce fatal visceral yellow fever in rhesus monkeys. This mouse-brain fixed neurotropic strain of virus has been used on a large scale in the French colonial populations in Africa.[19 20] The vaccine is essentially dried infected mouse-brain tissue which is resuspended in a solution of gum arabic and applied to the scarified skin.

Other investigators, largely as a result of animal experiments, considered the French neurotropic vaccine to be too virulent for human use. Consequently, Theiler and his associates carried out a long series of investigations which resulted in the chick-embryo-adapted 17D strain vaccine.[21] The 17D strain of virus originated from the Asibi strain and was derived by cultures as follows: 18 passages in minced mouse embryo/Tyrode's solution; 58 generations in whole chick embryo/Tyrode's solution; and 160 subcultures in chick embryo (head and spinal cord removed)/Tyrode's solution.

Inoculation of monkeys by neural routes showed that the 17D strain had to a great extent lost its power to produce fatal encephalitis between the 89th and 114th chick-embryo-tissue culture passages.[21] More extensive experiments in which rhesus monkeys were inoculated intracerebrally with the 17D virus showed that the incidence of fatal infection for this host is from 5 to 10%, and varies with parallel cultures of the strain.[22] In addition to losing neurotropism for mice and monkeys, the 17D strain became less viscerotropic for these animals. As a rule, monkeys inoculated with the 17D strain by extraneural routes showed no fever or other signs of illness, and only minimal amounts of virus could be demonstrated in their blood. Such monkeys developed specific antibodies and were solidly resistant to challenge with highly virulent strains of yellow fever. After extensive experimentation in monkeys, the 17D strain was used for human vaccination. With the loss of both neurotropic and viscerotropic properties, as demonstrated in monkeys, this seemed to be the virus strain of choice for human vaccination—a decision which, in the main, has been well justified. It should be mentioned, however, that the reason for the relatively rapid change in virulence of the 17D strain, which occurred between the 89th and 114th tissue culture passages, was and still is completely unknown.

Yellow fever vaccine is now produced from developing chick embryos. The vaccine consists of frozen and dried infected chick-embryo tissue reconstituted in sterile salt solution, and is injected subcutaneously in a 0.5-ml. dose.

Like smallpox, the yellow fever vaccine induces immunity by actually producing an infection in the vaccinated individual. Small quantities of active virus appear capable of producing immunity in a man.[23] The minimal quantity of virus in the finished vaccine has been set at 500 LD_{50} for white mice inoculated intracerebrally. The mild clinical reaction produced by yellow fever vaccine is rather typical of all living attenuated virus vaccines. Thus approximately 5% of vaccinated persons show, on or about the seventh day, a reaction consisting of malaise, headache, backache, and slight fever. This usually lasts only about 24 hours and is seldom severe enough to interfere with daily routine. Immunity, demonstrated by neutralizing antibody production, is manifest by the seventh to ninth day after vaccination. The titre of antibodies in persons vaccinated with 17D virus is as a rule low, but antibodies may be found by the seventh to ninth day after vaccination and they persist for considerable periods of time. Studies carried out by Dick and Gee[24] indicate an immunity persisting for at least nine years. The immune response may be less in children than in adults. Millions have been vaccinated with the 17D vaccine.[17] Perhaps the most conclusive demonstration of the effectiveness of yellow fever vaccination is the fact that since it was introduced no accidental cases of yellow fever have occurred in laboratory workers. Prior to the development of a vaccine such infections were extremely common and several cases were fatal.

The more recent studies of Hahn suggest that cutaneous application may provide a more effective and yet less expensive method of vaccination against this disease.[25] Hahn's work indicates that 17D chick-embryo vaccine applied topically in human beings induces a high degree of immunity within 10 days. This vaccine is prepared by grinding the virus-infected chick embryos with gum arabic solution and freeze-drying the mixture, which is rehydrated with saline or distilled water at the time of use. Additional experiments have been made with mixed vaccinia and yellow fever viruses. The combined vaccine has given encouraging results in field trials.

It should be noted that no chemical or physical method has been found for inactivating yellow fever virus—that is, for eliminating its pathogenicity and yet retaining its antigenic properties.[22]

Rabies

In an effort to develop a strain of rabies virus that could be used safely for immunization, Pasteur and his associates[26] passed the virus intracerebrally in series in a number of animal species. Intracerebral serial passage in rabbits produced a strain of rabies characterized by a very short incubation period. Such modified strains were called fixed, to differentiate them from the natural or street virus strains. After about 100 passages in rabbits the fixed virus had little lethal capacity when injected subcutaneously into dogs. After Pasteur many workers, too numerous to mention here, developed both living and killed types of rabies vaccines for use in various parts of the world. All of these vaccines were prepared from infected central nervous tissues, and suffered from the fact that they often gave rise to neuroparalytic reactions, as well as offering a relatively short span of immunity.

Seeking to overcome some of the shortcomings of the brain-tissue vaccines, the so-called Flury-strain vaccine was developed in my laboratory. Briefly, it is produced in developing chick embryos from a strain of rabies isolated by Leach and Johnson[27] from the brain of a girl named Flury.[28] The Flury strain is unique in that it is the only strain of rabies virus, so far as I know, that has been maintained entirely in non-mammalian hosts since its original isolation from human tissues. Johnson carried the strain for 136 serial passages in the brain tissue of 1-day-old baby chicks. He observed that the chick-adapted virus showed a lessened pathogenicity for rabbits, mice, and dogs. He also reported that although rabies could be induced in dogs by intracerebral inoculation of the chick-adapted strain, yet at necropsy no virus could be demonstrated in the salivary glands or saliva.[29] This was a most important observation, since if rabies virus is not present in the saliva of a rabid dog it is most unlikely that the dog could serve as a vector in transmitting the disease by biting other animals. Dr. Johnson very kindly made the 136th chick-brain passage of the Flury strain available to us. Dr. Hilary Koprowski and I succeeded in adapting the strain to grow in developing chick embryos.[30] The strain is pantropic for the chick embryo—virus being found in all embryonic tissues, including the blood.[31] Furthermore, even at low passage levels, the virus was relatively innocuous for guinea-pigs and rabbits tested by peripheral routes.

Following good results obtained in rabbits and guinea-pigs, extensive laboratory tests were carried out in dogs. These may be summarized by stating that dogs which have been inoculated intramuscularly with a single 3-ml. injection of a 33⅓% chick-embryo suspension show uniform resistance within 18 to 20 days to massive street-virus challenge inoculated bilaterally into the masseter muscles of the jaw. Animals immunized with Flury-strain vaccine resist challenge with street-virus strains not only of American origin, but also with strains isolated in Greece, India, and Central America (vampire bat origin).[32] The Flury strain is immunogenic only in its living state. No satisfactory physical or chemical method has been found that will inactivate the virus without destroying its antigenic capacity. Laboratory tests have been confirmed by extensive field tests in Georgia, in the State and City of New York, more recently in Malaya, and in a mass rabies control programme sponsored by the World Health Organization in Israel.[33] At present the Flury rabies vaccine is licensed and recommended for vaccination of dogs only, but impressive results have been obtained in the vaccination of other animals, particularly cats and cattle (cats received a 1.5-ml. dose, and cattle 7.5 or 15 ml.). All evidence to date indicates the superiority of intramuscular vaccination over the subcutaneous route.

Flury Strain Tests

The Flury strain of rabies virus is propagated in the developing chick embryo. The infected chick-embryo-tissue suspension is frozen and dried with stabilizers to preserve maximal viral activity. Each batch of vaccine is tested in three ways: for adequate virus content by intracerebral inoculation of mice; for freedom from other potential pathogens by inoculation into dogs, guinea-pigs, and mice; and for immunogenic capacity by street-virus challenge of vaccinated guinea-pigs. Good vaccines as a rule must contain approximately $10^{-3.5}$ LD_{50} as judged by intracerebral titration in mice. More than a million dogs have been vaccinated with the Flury-strain product, and in no instance has the modified virus showed a tendency to regain its original virulence and transmissibility.

After prolonged serial passage of the Flury strain in chick embryos, a marked decrease in its pathogenicity for laboratory animals was observed. Up through the 176th chick-embryo passage, the Flury strain consistently killed intracerebrally injected adult mice, with LD_{50} titres ranging from $10^{-4.5}$ to $10^{-5.5}$ or 10^{-6}. From the 178th to the 208th egg passages the Flury strain was devoid of lethal activity as measured by intracerebral injection of adult mice. Subsequent studies have revealed that the high passage levels of Flury virus in chick embryos have lost their pathogenicity for young adult mice, but have retained pathogenicity for suckling mice 8 days old or younger. What is more important is that the strain has apparently maintained its immunogenic capacity for dogs, guinea-pigs, and adult mice.

The finding that such a highly neurotropic virus as rabies can become so greatly attenuated in virulence and invasiveness is thought-provoking. The question arises, "Will the high-passage-level Flury virus retain its immunogenic capacity, or will this property be lost on continued passage in chick embryos?" One thing certain, however, is that the Flury strain will never regain its original virulence for dogs or other animals by continued serial passage in chick embryos. As a matter of fact, our problem will be to

preserve the immunogenic capacity of the strain for mammalian hosts. This is something we are fully aware of, and fortunately can control.

The Flury rabies vaccine unquestionably confers a solid degree of protection to vaccinated dogs for two- and three-year periods against a massive challenge dose of street virus, as shown by Tables III and IV.

TABLE III.—*Results of Immunity Test in Dogs Vaccinated 24 Months Previously with Flury Rabies Vaccine*

Authors	Type Vaccine	Mortality Ratio
U.S. Public Health Service in co-operation with Lederle	Avianized (Flury) Lederle	0/33 (0%)
	Controls (non-vaccinated)	18/33 (54·5%)

TABLE IV.—*Results of 39 Months' Immunity Test in Dogs Vaccinated with Different Types of Rabies Vaccine*

Authors	Type of Vaccine	Mortality Ratio
U.S. Public Health Service in co-operation with Lederle	Phenolized (commercial)	8/34 (23·5%)
	Ultra-violet (commercial)	7/30 (23·3%)
	Avianized (Flury) Lederle	0/30 (0%)
	Controls (non-vaccinated)	31/36 (86·1%)

Table IV shows a comparative immunity test in dogs vaccinated 39 months previously with Flury living-virus vaccine or with phenolized or ultra-violet-inactivated commercial vaccines prepared from nervous tissues.[34 35] Frankly, we were surprised that the killed vaccines—the phenolized and ultra-violet preparations—conferred as good protection as the three-year challenge test revealed. However, the Flury living virus-vaccine obviously gave the best performance on challenge.

In additional studies,[36] it has been determined that hyper-immune serum may supplement Flury-strain rabies vaccine in cases of extremely severe exposure, and that immune serum does not interfere with or block the immunizing capacity of the living virus agent.

Results of work looking towards the use of the Flury-strain vaccine in man indicate that the product will be safe for human immunization. Further experiments have to be made, however, to determine the optimal dosage and time of injection.

Unquestionably, the Flury rabies vaccine, with its high-degree long-lasting immunizing capacity and its relative lack of neuroparalytic factors, constitutes a major weapon in our armamentarium against infectious agents.

Blue-tongue

My laboratory has recently become interested in a hitherto exotic disease known as blue-tongue, since the disease is now well established in the sheep population of a number of our western States.[37 38 39 40]

Blue-tongue is an infectious inoculable viral disease of cattle and sheep, characterized by catarrhal inflammation of the mucous membranes of the mouth, nose, and intestines, and often associated with inflammation of the coronary bands and sensitive laminae of the hoofs. The swollen and inflamed mouth and tongue take on the purple or dirty blue colour from which the disease derives its name. The disease is not transmitted by contact, but by biting insects. The infectious agent is an extremely resistant virus which remains viable for years in the fluid or dry state. At least four and possibly five or more immunologically distinct viral strains are currently recognized, yet they all produce the same clinical symptoms. Animals may carry the virus for weeks or even months after recovery, and are immune to subsequent infection with the homologous viral strain.

For many years blue-tongue was thought to be strictly an African disease. It has now occurred in Cyprus, Israel, and Turkey, and more recently in the western United States.[41]

Of the laboratory hosts commonly used for experimental work, only suckling white mice, injected intracerebrally, and developing chick embryos are apparently susceptible.

The blue-tongue vaccines in use to-day are based on the original findings of Alexander and his associates[42 43 44 45] that any strain of the blue-tongue virus apparently will grow in the developing chick embryo provided careful attention is paid to the temperature of incubation.

By serial passage through chick embryos, virulent strains of blue-tongue virus are rapidly attenuated to a point where practically no clinical reaction is produced in sheep. As would be expected, each virus strain must be studied separately to determine optimal conditions, but attenuated strains retain their full antigenic capacity for inoculated sheep, provided the chick-embryo material used for vaccine is from a relatively low serial passage level. This is an extremely important point in the preparation not only of blue-tongue but of practically all other chick-embryo-propagated and attenuated vaccines. Long-continued passage in the foreign host—chick embryo in this case—will bring about over-attenuation of the agent to a point where it ceases to be a good immunogenic antigen. Thus great care must be taken at all times to use seed virus of the proper serial passage level in order to obtain an effective vaccine.

Alexander and his co-workers,[44 45] also made the important observation that once a strain of blue-tongue virus had become attenuated by chick-embryo passage its virulence could not be restored or enhanced by 11 consecutive serial passages in sheep. I might add that a similar observation has been made recently by my associate Koprowski with our rabbit-attenuated strain of hog cholera virus. Koprowski[47] was unable to restore or enhance the virulence of the virus for swine by passing the attenuated strain for 10 consecutive serial passages in that species.

The present blue-tongue vaccine produced at Onderstepoort[45] is a quadrivalent living chick-embryo-attenuated product. Four different virus strains are grown separately in chick embryos, then pooled. The resulting vaccine contains approximately 250 chick-embryo infecting doses for each strain per 1-ml. dose.

In a personal communication,[45] Dr. Alexander, of South Africa, has advised that a strain of California origin has been found, in preliminary tests, to be relatively avirulent for sheep yet remarkably broad in its antigenic coverage. In these early tests the California strain developed good protection in vaccinated sheep against subsequent challenge with three antigenically different Onderstepoort strains. If subsequent tests confirm these results the problem of producing a blue-tongue vaccine of polyvalent antigenicity will be made much simpler.

As with yellow fever and Flury-strain rabies vaccines, no satisfactory chemical or physical method has been found for inactivating blue-tongue virus without destroying its immunogenic properties.

Poliomyelitis

I will now discuss some of the problems facing us in preventing poliomyelitis. At once I wish to make it clear that gamma globulin (immune serum globulin) is not the answer to the problem of securing long-term protection against poliomyelitis. The various shortcomings of immune-serum-globulin therapy and the attendant difficulties have been discussed in detail elsewhere,[49] so I will refrain from doing so here.

Without doubt, there is only one thing to do, and that is to put all possible effort into developing a practical and safe vaccine which will give long-term and solid protection against the disease. The problem is tripled by the fact that there are at least three main immunological types of the poliomyelitis virus. However, it must be remembered that the problem is really no more complex in this respect than

the one faced by investigators in the field of veterinary medicine in developing vaccines against blue-tongue of sheep and foot-and-mouth disease of cattle. We recognize four and possibly five immunological types of blue-tongue, and apparently six different antigenic types of foot-and-mouth disease (at least three of European origin and three African). The problem was met in the case of blue-tongue with the polyvalent living chick-embryo-adapted vaccine already described; and in the case of foot-and-mouth disease by a polyvalent killed vaccine utilizing virus strains cultivated in explanted bovine tongue epithelium.[50 51 52 53 54]

Regardless of whether we wish to prepare a living attenuated or an acceptable "killed" vaccine, the problem is resolved to one of finding a plentiful and satisfactory source of tissue in which the virus will readily grow to high titre. Furthermore, the tissue used must not offer a potential source of any other pathogenic infectious or malignant agent for man. For killed vaccines, multiple injections of which will undoubtedly be necessary to produce a good immune response, extra care must be taken to avoid possible anaphylaxis and organ-tissue damage. Any adjuvant used must likewise be thoroughly tested and shown to be free of any potential carcinogenic or organ degenerative activity before it is recommended for large-scale use in man.

Present Progress

Now let us see what progress has been made in solving the problem of developing a practical and safe immunizing weapon against poliomyelitis.

Prime credit must be given to Enders, Weller, and Robbins,[55 56] who first demonstrated that poliomyelitis viruses not only propagate in cultures of human embryonic and adult non-nervous tissues but also produce a cytopathogenic change therein. This latter finding makes it possible to recognize the presence of virus without the need of resorting to animal inoculation. The subsequent discovery that various monkey tissues, particularly the kidneys, provide a good culture medium for all three antigenic types of poliomyelitis still further opened up opportunities for study in the field. This approach for studying various aspects of the poliomyelitis problem, such as virus detection, propagation, assay, antibody quantitation, preparation of diagnostic antigens, and experimental vaccines, has been used by many workers, including Salk and his associates at the University of Pittsburgh,[57 58 59] Melnick at Yale,[60 61 62 63 64] Syverton at the University of Minnesota,[65 66 67 68 69] Rhodes at the University of Toronto,[70 71 72] and Evans at the University of Washington.[73 74]

Recently, Salk[75] reported experiments in which he vaccinated 161 human volunteers with formalin-"killed" tissue-culture virus vaccines prepared from monkey kidney or monkey testes. An aqueous vaccine given intradermally induced an antibody response only against Lansing type 2 virus. However, a water-in-mineral-oil emulsion type "killed" vaccine inoculated deep intramuscularly was claimed to induce antibody response against all three types of poliomyelitis virus (Brunhilde, Lansing, and Leon). The vaccine contained only 0.1 ml. of tissue culture material of each of the three types. If it were true that such small quantities of inactivated virus would actually induce a primary antibody response in human beings, we would indeed have a very effective and practical vaccine available. Unfortunately, however, this is not the case. It should be noted that all of Salk's antibody titres were reported on sera taken a very short time after vaccination—never longer than four to seven weeks. Of greater importance is the fact that significant antibody titres were found in most of the vaccinated subjects prior to vaccination: 6 of 12 against type 2, 7 of 16 against type 3, and 15 of 15 against type 1. It is well known, of course, that it takes much less antigen to demonstrate a booster effect than it does to stimulate a primary antibody response in persons who have never had previous exposure to the agent. Thus analysed, Salk's results cannot be regarded as too favourable or impressive.

Need for a Satisfactory Assay Method

The basic information which should be in hand before any vaccine is tested on a large scale in human beings is, quite frankly, not yet available. Even the first step of developing a satisfactory and reproducible assay method in experimental animals has not been taken. None of the tedious and laborious—yet necessary—qualitative and quantitative tests in suitable experimental animals that are usually required of any new vaccine before it is used in either human or veterinary medicine have been performed. Such basic tests are absolutely essential to evaluate a vaccine.

Caution must be taken to prove that a vaccine contains a sufficient amount of antigen to make it a good immunizing agent rather than a sensitizing agent. In studies carried out with killed Rocky Mountain spotted fever and epidemic typhus fever vaccines, we found[76] that preparations which did not contain enough antigen to produce a good immunogenic vaccine actually sensitized the vaccinated animals and made them more susceptible to challenge than the non-vaccinated controls. Thus, if adequate quantitative studies are not carried out on proposed poliomyelitis vaccine preparations to ensure that they actually contain a sufficient amount of antigen, more harm than good could result from their use.

The recent findings of Scherer, Syverton, and Gey[69] that all three types of poliomyelitis viruses can be grown in a strain of human malignant cells (Héla strain) raises the question of whether such cultures could be used without danger as a source of vaccine. This question cannot be answered with certainty at present, but I am sure that no one would recommend the use of neoplastic cells or tissue as a medium for producing poliomyelitis vaccine.

At this point, I wish to state that there is no question whatsoever about the merit of tissue culture for research purposes. It can be gainfully used for many problems, such as isolation, identification, and propagation of infectious agents, quantitation of antibodies and assay of infectious agents by the neutralization technique, and for the development of virus variants that may be adapted to new and ordinarily non-susceptible hosts. My laboratory is particularly interested in the latter application because of its almost unlimited possibilities. A mouse-adapted variant strain of type 1 poliomyelitis virus (Mahoney strain) was derived from tissue culture material by Li and Schaeffer.[77] Further observations concerning the pathogenic spectrum of this strain are awaited with great interest because of the rapidity with which this virus apparently lost most of its virulence for intracerebrally inoculated monkeys.

Two Promising Leads

Returning to the problem at hand, a review of the literature indicates that the two most promising leads to follow for inducing immunity to poliomyelitis are the intramuscular and oral routes of administering the virus. I am of the opinion that probably the most logical and practical way to immunize against poliomyelitis is to use the natural portal of entry—the oral route—employing an attenuated living virus under qualitatively and quantitatively controlled conditions. This is the eventual goal of my laboratory, and we intend to continue our efforts in this direction until success is achieved. However, the road ahead is long and difficult, and we may have to content ourselves temporarily with a less satisfactory product until the present obstacles are overcome. My associates Koprowski *et al.*[13 14] have carried the work a step further along the way by feeding a living rodent-adapted poliomyelitis virus to two sizable groups of human volunteers. The virus consisted of a suspension of brain and spinal-cord tissues of cotton-rats infected with the TN strain type 2 poliomyelitis virus, which had been shown to have lost much of its intracerebral virulence for monkeys. The individuals were observed carefully: none had a temperature rise or any sign of illness. Most of them became intestinal carriers of the virus for a

short time. Practically all of them who were not initially immune developed neutralizing antibodies to the homologous Lansing type virus, but not to the heterologous Brunhilde type.

While I believe the use of living attenuated virus offers the most logical and hopeful approach towards solving the poliomyelitis problem, I do not believe that the virus should be propagated in infected mammals or in infected mammalian explanted tissues until other approaches have been exhausted. Thus I am not in accord with Sabin's recent suggestion[78] of possibly using avirulent or "non-paralytogenic" poliomyelitis strains cultivated in monkey nonnervous tissues as a source of living attenuated vaccines for human use. Those responsible for producing vaccines on a large scale recognize that such infected mammalian tissues present the potential danger of being contaminated with other viruses or microbic agents which are infectious for man. These include lymphocytic choriomeningitis, infectious hepatitis, Sabin's B virus, encephalomyocarditis, tuberculosis, etc. The cost of testing to determine adequately the purity, safety, and identity of the product would be exorbitant if not prohibitive. These charges alone would tend to defeat our purpose of producing a practical vaccine that everyone can afford.

Without doubt the poliomyelitis problem would be greatly simplified if we could use the developing chick embryo as culture medium. The chick embryo is one of nature's best tissue-culture media, with the prime advantages of always being readily available in unlimited quantities, easily handled in the laboratory, relatively inexpensive, and, above all, free from micro-organisms potentially pathogenic for human beings. Furthermore, since the chick embryo is not a natural host for poliomyelitis virus, variant strains established in this medium will not regain their original virulence for men.

The MEF1 Strain of Virus

As you know, our faith in this approach already has been rewarded by the successful adaptation of the MEF1 strain Lansing type virus to the chick embryo.[49 79 80 81] In this instance the variant was obtained by carrying the virus for at least 119 consecutive serial passages in suckling hamster brain tissue.[82] I am fully aware that the task of getting the Brunhilde and Leon strains similarly adapted is not an easy one, but I am confident it can and will be done. The successful fulfilment of this assignment will be worth whatever "blood, sweat, and tears" have to be expended. All I can say at present is that progress is being made; not as fast as we would like to have it, of course—yet we are advancing.

At least five separate substrains of the MEF1 virus have now been carried through more than 100 consecutive serial passages in chick embryos. LD_{50} titres of the infected chick embryo suspensions, measured by intracerebral titration in mice, range from 10^{-5} to 10^{-6} or slightly higher. The major changes in the properties of the virus brought about by adaptation to the rodent host are retained essentially unchanged in the avian host for a considerable number of passages. However, there is evidence that long-continued passage in chick embryo results in gradual loss by the virus of some of its original antigenic characteristics for primates. Thus, as in yellow fever, Flury-strain rabies, and bluetongue viruses, great care will have to be taken to use only those chick-embryo passage levels which secure optimal results as a vaccine.

One of the unusual properties of the adapted MEF1 strain of virus is that the chick embryo shows little, if any, sign of infection. Embryos do not die from acute infection, as so often happens with other neurotropic viruses, and the great majority die just prior to hatching time. Maximal growth of the virus apparently takes place in the embryo itself. The optimal time to harvest the infected tissues is on the fourth or fifth day following inoculation.

At present we are studying the antigenic characteristics of certain substrains of the chick-embryo-adapted virus in relation to their intracerebral safety and immunogenic capacity by the intramuscular and oral routes for primates —particularly cynomolgus and rhesus monkeys and chimpanzees. These studies are still in their infancy. However, we have demonstrated that experimental vaccines, of little or no "paralytogenic" and no lethal effect when injected intracerebrally into rhesus or cynomolgus monkeys, produce an immunogenic response indicated by neutralizing antibodies when given intramuscularly but not orally to these same hosts.[79 83] The same vaccines, whether given intramuscularly or orally, apparently activate a good antigenic response in chimpanzees.[79] Neutralizing antibodies in significant titres appeared by the 14th day and persisted through the 127th day. Oral revaccination with the same preparation on the 127th day gave a good booster effect to three out of four chimpanzees. These studies are being continued and extended.

Conclusion

In summary, I wish to emphasize that from a practical standpoint the use of living attenuated viruses as immunizing agents is unquestionably the best method for securing long-lasting and safe protection. Many people are still uncertain about accepting the use of living virus vaccines in preventive medicine, yet the fact remains that the outstanding successes of specific immunization have been with living attenuated virus vaccines: smallpox, yellow fever, rinderpest, rabies, and blue-tongue. Present evidence indicates that attenuated living virus vaccines induce immunity through the same mechanism used by nature: by producing inapparent subclinical infections. Both the virus and the host are factors to be considered in bringing about immunizing infections, but by suitable qualitative and quantitative procedures we now are able to control changes in virus properties and make them suit our needs.

Finally, I wish to repeat that a tested practicable vaccine for poliomyelitis has not yet been produced. Furthermore, no one can now predict when such a practical, safe, and satisfactory vaccine will become available. It would be useless to make such a prediction now, because a tremendous amount of basic information still must be gained. However, I am optimistic. The tools and methods are at hand to do the job. I am confident that before long we will succeed in propagating all three major types of poliomyelitis virus in the developing chick embryo, and achieve our goal of a living attenuated virus vaccine which will confer durable protection against poliomyelitis. Thus another potent weapon will be added to our arsenal against disease.

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THE DIAGNOSIS AND TREATMENT OF HYPOPITUITARISM

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During the past three years we have studied nine cases of hypopituitarism and endeavoured to find a satisfactory scheme of treatment using A.C.T.H. and cortisone in addition to preparations of the thyroid gland and testosterone. In the course of this investigation we have been struck by the distressingly long period, sometimes extending over a number of years, that may elapse between the onset of symptoms and the establishment of the diagnosis. Despite the classic papers of Sheehan and his associates (Sheehan, 1939; Sheehan and Summers, 1949; Cooke and Sheehan, 1950), it appears that the syndrome of hypopituitarism may still pass unrecognized for a considerable time after the patient has sought medical aid, possibly owing to the confusing variation in the impairment of function of the thyroid gland, the adrenal cortex, and the gonads that may exist in different patients.

Since the treatment of hypopituitarism with A.C.T.H. and cortisone promises to be a considerable advance on previous methods, an early diagnosis assumes more importance, and we feel it worth while to record some observations on the clinical picture, a brief account of the investigations likely to be of value in establishing the diagnosis, and the results of treatment with A.C.T.H. and cortisone, sometimes combined with other hormones, for periods up to two years.

Material.—This study is based on seven women and two men whose ages ranged from 32 to 63 years, with an average of 47. Five of the women (Cases 1–5) had suffered from severe haemorrhage after childbirth, and a post-partum necrosis of the pituitary gland was likely. The exact nature of the pathological process damaging the pituitary gland is unknown in the other four cases, although one patient had been treated for syphilis some years previously (Case 9). One patient died during the course of the investigation (Case 1).

Clinical Picture

The difficulties of an early diagnosis are perhaps illustrated by the fact that nine patients between them paid over 30 visits to different hospitals or hospital departments before the diagnosis of hypopituitarism was finally made. The average duration of symptoms was over 10 years, and, unless there was a clear history of haemorrhage during childbirth followed by absence of lactation and scanty periods or amenorrhoea, it was difficult to determine accurately the date of onset of the disease. The clinical picture varied from patient to patient, but the following features were the most constant.

Tiredness.—All patients complained of feeling tired, and it was usually this symptom that first prompted them to visit a doctor. A diagnosis of anaemia was often made, and some tonic prescribed. The tiredness continued but rarely became incapacitating, and after a time these patients became accustomed to feeling tired and struggled on as best they could, aware that there was something the matter

with them but disappointed by repeated visits to doctors or hospitals. The disease is essentially a chronic one, and several patients stated that they had almost forgotten what it was like to feel well.

Mental State.—Some degree of mental inertia was noted in all patients, and the blunting of the mental faculties appears to compensate for the discomforts caused by other features of the disease and the placid acceptance of ineffective treatment over a number of years. There was, however, a considerable variation in the degree of mental change. One patient had been admitted to a mental hospital (Case 4), whereas another was still managing a thriving business despite the fact that he had had symptoms of hypopituitarism for 12 years (Case 9). Between these extremes four patients were carrying out household duties (Cases 1, 2, 6, and 7) and three were chronic invalids being cared for by relatives (Cases 3, 5, and 8).

Sensitivity to Cold.—All patients complained of feeling cold even in summer weather, and it was noticed that some of them arrived at the out-patient department wearing too many clothes for the season of the year. When admitted to hospital they lay in bed under numerous blankets with only a small area of the face showing, and one brought with him a nightcap which he had worn for a number of years. Erythema ab igne was a common finding in women patients, although the areas were not pigmented.

Loss of Libido.—Hubble (1952) pointed out that the sex hormones are the first to be affected in hypopituitarism and may antedate clinical evidence of failure of the thyroid gland or the adrenal cortex by as long a period as 20 years. It is unfortunate that there is a natural reluctance to inquire into a patient's sexual life, although Sheehan and Summers (1949) noted that female patients suffering from hypopituitarism lose their normal bashfulness, an observation which we can readily confirm. Loss of libido is an important early symptom, and both male patients were impotent. Female patients who continued intercourse as part of their marital duties derived little, if any, pleasure from it and rarely obtained an orgasm.

Amenorrhoea.—Complete amenorrhoea was noted in five women but had been of gradual onset in three. One woman had normal periods and became pregnant two years after a clinical diagnosis of hypopituitarism (made by Dr. C. R. St. Johnston) had been confirmed by numerous investigations (Case 3). The pregnancy went to full term, but subsequently no improvement in her condition was noted, and her periods began again in a normal manner. Such incidents, although exceptionally rare, are mentioned by Sheehan and Murdoch (1938).

Loss of Hair.—One female patient (Case 6) lost all the pubic and axillary hairs at the age of 19 but never thought to mention the fact to any of the practitioners whom she consulted during the next 20 years. In general, patients are reluctant to admit the loss of hair on any part of the body, and neither of the male patients volunteered the information that they had stopped shaving some time previously. The loss of pubic hair may not be complete, but nevertheless it was striking enough to call for comment in all our patients, and served as a useful pointer to the diagnosis of hypopituitarism.

Appearance.—The lack of animation of the face, the waxy pallor and slight puffiness of the skin, and the thinning of the eyebrows and of the hair on the head combine to give an appearance which looks grotesque in young and middle-aged patients and is easily recognizable. In older patients a closer inspection may be necessary, since the contrast with other patients of the same age group is less obvious. The loss of skin pigment is widespread and the areolae of the breasts should be inspected. Familiarity with the facies of hypopituitarism is a considerable aid in the clinical diagnosis, but such familiarity may be difficult to acquire, as the disease is not common and our experience of successive house-physicians suggests that some medical students may complete their hospital training without an opportunity of observing a case. The skin is dry owing to the absence of sweating, and feels smooth and soft. As Sheehan and Summers (1949) have emphasized, patients suffering from hypopituitarism are not emaciated, and three patients in the present series had a rather plump appearance. The body weights of the remaining six were also within the normal range for their height and age.

Speech.—A slow soft monotonous type of speech was noted in six patients, but in the other three no special comment could be made, although their speech became more articulate after treatment. The slowness of the speech appeared to be related to the degree of mental lethargy, and two patients were apt to tail off in the middle of a sentence as if they had not enough mental energy to complete it (Cases 4 and 8).

Routine examination of the various systems added little to the clinical picture. The pulse rate varied from 62 to 80 a minute, with an average rate of 70. The systolic blood pressure ranged from 90 to 155 mm. Hg, with a mean of 115 mm. A low-voltage electrocardiogram with rather flat T waves was recorded in six cases and a normal electrocardiogram in three. A mild degree of normochromic anaemia was common, but was less than might have been expected from the appearance of the patient. The haemoglobin varied from 62 to 101%, with a mean of 83%.

Biochemical Investigation of Hypopituitarism

Sheehan and Summers (1949) stated that a confident diagnosis of complete hypopituitarism could usually be made from a short clinical examination. They considered that in severe cases the biochemical tests were chiefly of academic interest and for assessment of the severity of the disease. In mild cases the diagnosis could be very uncertain. Fraser and Smith (1941) thought that mild cases of hypopituitarism might be confused with other cachexias, and biochemical confirmation was usually required. They advocated the use of the insulin-tolerance test and the estimation of urinary 17-ketosteroids as aids in the diagnosis of hypopituitarism. Oelbaum (1952), in a study of six cases of hypopituitarism from post-partum necrosis, concluded that biochemical investigations in hypopituitarism are not of great assistance in diagnosis as they are positive only when the clinical diagnosis is already obvious, at least to the initiated.

Table I shows the biochemical investigations carried out on our patients. It will be seen that there is a high proportion of abnormal results, particularly in the basal metabolic rate, the urinary 17-ketosteroids, the insulin-tolerance test, and the Kepler test. This prompted us to inquire further into the usefulness of these tests in the diagnosis of hypopituitarism.

TABLE I.—*Biochemical Investigations*

Case:	1	2	3	4	5	6	7	8	9
Sex	F	F	F	F	F	F	F	M	M
Age (in years)	32	38	41	40	56	52	63	50	52
Duration of symptoms (in years)	11	10	7	11	26	33	10	4	12
B.M.R.	43	−43	−40	29	−17	35	−36	−40	−33
Insulin-tolerance test	Pos.	Pos.	Pos.	Normal	—	Pos.	Pos.	Pos.	Pos.
Urinary 17-ketosteroids, mg. day	2·5	1·8	Nil	1·2	0·1	0·7	Nil	0·1	1·8
Kepler test	Pos.	Neg.	Pos.	Pos.	—	Pos.	Pos.	Pos.	Pos.
Fasting blood sugar (mg./100 ml.)	71	79	68	90	86	95	72	91	83
Cholesterol (mg./100 ml.)	325	533	420	420	450	248	190	200	287
Serum sodium (mEq/l.)	131	143	137	115	132	136	140	135	129
Serum potassium (mEq/l.)	5·0	5·3	4·6	4·3	4·3	4·2	5·0	4·6	4·4
Serum chloride (mEq/l.)	98	107	102	85	94	104	106	105	92

We have collected the biochemical results in the 51 cases abstracted from the literature and included our nine cases to make a total of 60. All the cases from the literature have been published in the last 12 years—the majority of them chiefly in British journals in the last four years; the cases abstracted were those with an adequate history and with reasonably full biochemical investigation.

Of the 60 cases, 37 followed severe post-partum haemorrhage, 7 resulted from tumour, and 16 were of unknown

or doubtful aetiology. The age at diagnosis ranged from 19 to 64 years and their history varied from three months to thirty-six years with an average of eleven years. There were 45 females and 15 males. In the investigation of these 60 cases the three biochemical tests most frequently chosen out of a number of tests of pituitary function were the basal metabolic rate, insulin-tolerance, and urinary 17-ketosteroids.

In Table II these tests are treated individually, and the number of cases in which the test was used and the number of cases in which the test was abnormal are recorded. In each of the tests between 85 and 90% of the cases tested gave abnormal results.

TABLE II

Test	No. of Cases Tested	No. of Abnormal Cases
B.M.R. (abnormal if less than −10% of normal) ..	54	48
17-ketosteroids (abnormal if less than 2 mg./day) ..	54	47
Insulin tolerance (interpretation as by Fraser and Smith, 1941)	45	38

Table III shows the results obtained with a combination of all these tests. It will be seen that two out of three tests have proved abnormal in 37 out of 40 cases of hypopituitarism reported during the past few years, and their

TABLE III

Total No. Investigated	No. with All Three Tests Abnormal	No. with Only Two Tests Abnormal	No. with Only One Test Abnormal	No. with None Abnormal
40	30	7	1	2

value in the investigation of suspected cases seems firmly established. From the few but increasing number of cases in which the Kepler test has been performed, and from our own results, it appears that it is a most useful test of adrenal function. The histories of our patients emphasize that the clinical diagnosis is not always obvious even to general physicians or psychiatrists, and we suggest that more use should be made of biochemical tests of pituitary function in cases of general debility or gradual failing of mental powers.

Treatment

Several favourable reports have recently been published on the treatment of hypopituitarism, usually for short periods, with A.C.T.H. and cortisone (Summers and Sheehan, 1951; Robertson and Kirkpatrick, 1951; Rolland and Matthews, 1952; Hart, 1953; Aber *et al.*, 1954). We first started treating some of our patients with A.C.T.H. and cortisone in the early months of 1951, when supplies were available from the Ministry of Health. The following results are based on three years' experience with these hormones; during this time we have changed from one scheme of treatment to another and, in addition, used preparations of the thyroid gland and methyltestosterone.

A.C.T.H.

A daily dose of 25–40 mg. of A.C.T.H. is a satisfactory form of treatment, and we have had gratifying results in eight patients despite the fact that the Thorn test carried out before treatment did not always suggest that there would be a striking response to A.C.T.H. Within 48 hours of receiving injections all patients became more active both mentally and physically, and experienced a sense of well-being which far exceeded any effects caused by A.C.T.H. when given for other conditions. Patients suffering from hypopituitarism begin to take interest in their surroundings, their speech becomes more distinct, blankets are cast off the bed; and many are the expressions of deep gratitude by them and their relatives.

Unfortunately, the stimulation produced by A.C.T.H. does not last long, and all our patients relapsed to some extent within 10 days of the cessation of injections. After four weeks relapse was complete. In Case 1 treatment was continued for over three months with an average daily dose of 45 mg., but a relapse occurred just as quickly as after a shorter course.

We had three unpleasant experiences when we were using doses of 40 or 60 mg. of A.C.T.H. daily. We think that each was caused by water retention, and it is probable that the early batches of A.C.T.H. received in this country were contaminated with pitressin, which contributed to the disturbance of water balance. The Chart shows the urinary volume and urinary sodium excretion before and during the first 11 days of treatment of Case 3. Similar biochemical changes were noted in Cases 1 and 2. The urinary sodium and volume increased for the first few days after treatment; this was followed by a sudden fall and then an increase. Over this period of retention followed by diuresis the patient complained of severe headache and looked bloated.

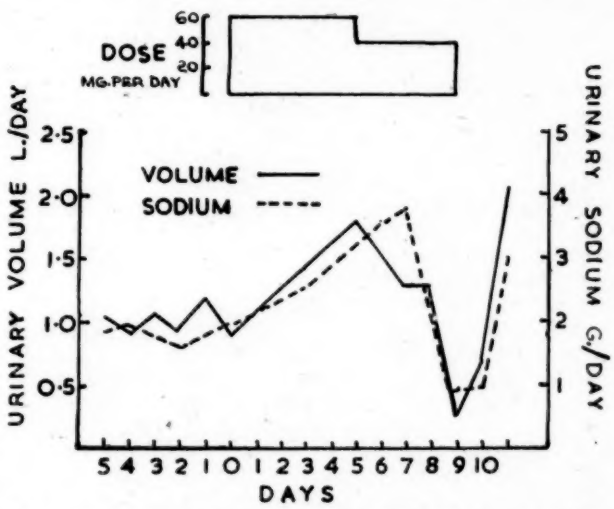

Chart showing the changes of urinary volume and urinary sodium during A.C.T.H. treatment of Case 3.

Cerebration became disordered and Case 1 was stuporous. Recovery from the state of water retention was uneventful after injections of A.C.T.H. had been stopped or the dose reduced, but the experience so frightened Case 2 that this patient refused any further treatment despite her continued ill-health from the disease. Bartter *et al.* (1950) and Knowlton *et al.* (1950) reported similar experiences during treatment with A.C.T.H., but we would emphasize that severe water retention is not a common complication and we did not encounter it during the later part of the investigation, when we were using smaller amounts of different batches of A.C.T.H. Nevertheless, we consider that the first course of A.C.T.H. should be given while the patient is in hospital, so that the urinary volume can be checked daily and a careful watch kept for signs of water retention.

We have not treated any patient with A.C.T.H. for longer than eight months, and we have now given up this method in favour of replacement therapy with cortisone and thyroid gland. On the whole, however, A.C.T.H. proved a considerable advance on any treatment we had used in cases of hypopituitarism before A.C.T.H. and cortisone were available, and, provided arrangements can be made to maintain stimulation of the pituitary gland with injections of A.C.T.H. once or twice weekly, there seems to be no reason why satisfactory treatment cannot be continued indefinitely. Aber *et al.* (1954) report three patients who are being maintained in good health with weekly injections of 40 units of "acthar gel."

Cortisone

We have treated eight patients with cortisone, given either by intramuscular injection or in tablet form. Treatment started with a daily dose of 50 or 75 mg., which was reduced after a few days to a daily maintenance dose of 12.5, 25,

or 37.5 mg. With the exception of Case 5 the immediate results of treatment with cortisone were excellent, and after a few days' treatment all patients showed a striking clinical improvement, which was indistinguishable from that obtained in the same patients with A.C.T.H.

We had an unfortunate experience with Case 5, who drifted into coma while receiving 50 mg. of cortisone daily. This lady of 56 years had suffered from hypopituitarism for many years, but there was no history of a previous attack of coma. She had responded well to A.C.T.H., but relapsed completely ten days after injections were discontinued. She was then given 50 mg. of cortisone daily, and after three doses appeared to be responding. On the fourth day, however, she became listless, and gradually sank into coma during the next four days, injections of cortisone being continued daily. The blood electrolytes were followed closely, but no significant changes were noted. The serum sodium remained around 138 mEq/l. and the serum potassium 5 mEq/l. The blood sugar was 160 mg./100 ml. The striking finding was a gradual fall in the rectal temperature to 87° F. (30.6° C.) (measured with a bacteriological thermometer) when she was in coma. Injections of cortisone were stopped, and fortunately she responded well to warmth applied by electric cradles. We believe that the attack of coma was of the myxoedematous type described by Sheehan and Summers (1952), and it is interesting that it should apparently have been precipitated by treatment with cortisone. After recovery this patient was given 25 mg. of cortisone together with ½ gr. (32 mg.) of thyroid gland daily, and there have been no further episodes of coma during the 16 months she has now received this treatment.

Cases 3, 4, and 8 were maintained on 25 mg. of cortisone daily for periods of three to six months, and during the greater part of that time they were carrying out their normal duties at home and attending hospital at monthly intervals for survey. Although the improvement in their health was most gratifying and they no longer required the assistance of relatives to run their homes, their facies appeared myxoedematous and, indeed, more so than before treatment with cortisone. Re-examination of the basal metabolic rates in Cases 3 and 8 revealed figures of −35 and −20%. This was obviously not satisfactory, and it seemed likely that further improvement could be effected by adding extract of thyroid gland to the daily dose of cortisone. We have subsequently changed the treatment of all patients who were receiving cortisone alone to a mixture of cortisone and thyroid.

Cortisone and Thyroid Gland

We have treated seven patients for periods of between nine and twenty months with daily doses of cortisone and thyroid given in tablet form. The daily amounts which each patient was receiving at the time of writing are shown in Table IV.

TABLE IV

Case	Cortisone	Thyroideum *B.P.*	Period of Treatment
3	25 mg.	1 gr. (65 mg.)	20 months
4	12·5 mg.	½ gr. (32 mg.)	19 ,,
5	25 mg.	½ gr. (32 mg.)	16 ,,
6	12·5 mg.	½ gr. (32 mg.)	10 ,,
7	12·5 mg.	1½ gr. (97 mg.)	9 ,,
8	12·5 mg.	1½ gr. (97 mg.)	17 ,,
9	25 mg.	1 gr. (65 mg.)	10 ,,

We suggest that treatment should start with a daily dose of 25 mg. of cortisone and ½ gr. (32 mg.) thyroid and that these amounts be altered during the first few months of treatment rather by the method of trial and error. Patients suffering from hypopituitarism usually feel so much better after a few doses of cortisone alone that the addition of thyroid may not seem necessary. Nevertheless, we have found that further improvement could be obtained in every case, and we have also reduced the dose of cortisone from 25 mg. to 12.5 mg. daily in four cases without any deterioration in their condition. So far there have been no complications during this form of treatment, which has now been given to seven patients for an average period of fourteen months.

Case 6 had previously suffered from pulmonary tuberculosis, but the radiological changes in both lungs remained stationary, and as cortisone was being given as a replacement the usual qualifications regarding its use for long periods hardly apply. Patients were seen at monthly or two-monthly intervals as out-patients, when adjustments in dosage could be made. Neither the age of the patient nor the length of duration of symptoms appears to preclude an excellent response. Case 5 started treatment at the age of 56, having suffered from symptoms of hypopituitarism for twenty-six years and having been a chronic invalid for several years. She now leads a normal life, carrying out her own housework and occasionally looking after her grandchildren. There can be few more gratifying experiences than the diagnosis and successful treatment of a case of hypopituitarism of many years' standing.

Addition of Testosterone

We have recently added amounts of methyltestosterone varying from 25 to 50 mg. daily to the maintenance dose of cortisone and thyroid in Cases 3, 4, 8, and 9. In both male patients (Cases 8 and 9) there has been an increase in libido and strength of the erection and in the growth of pubic hairs. No effect has been noticed so far by either of the female patients, who were satisfied by the increase in libido caused by cortisone. Case 3 continues to have regular periods but has not conceived again since her pregnancy four years ago.

Water Balance and Coma in Hypopituitarism

Throughout the whole investigation we have been continually reminded of the abnormality of water balance in hypopituitarism. This has been the subject of several reports, and Slessor (1952) has shown evidence of an increased antidiuretic hormone in the blood of patients with secondary or primary adrenal deficiency. Lewis (1952), however, thinks the abnormality is caused by defective function of the osmoreceptors or of the renal tubules, or to both of these. Prunty (1953) regards both A.C.T.H. and cortisone as having a direct action on water balance, apart from the contamination with pitressin which may occur in some batches of A.C.T.H. Robertson (1951), in one case, found no effect on water metabolism during A.C.T.H. or cortisone therapy. Chalmers and Lewis (1951) and Oleesky and Stanbury (1951) showed normal handling of administered water during cortisone therapy.

Our experience is similar to that of Aber *et al.* (1954) in that the daily urinary output in severe cases of hypopituitarism may be variable and on occasions exceptionally low: volumes of less than 500 ml. a day are common, and Case 5 sometimes did not pass water at all during a twenty-four-hour period. All patients treated with cortisone have had an immediate increase in the urinary volume, which has remained steady at two litres or more a day during treatment. This suggests that the gratifying clinical improvement obtained by treatment with cortisone may be related to changes in water metabolism.

Sheehan and Summers (1952) consider that, despite the relative uniformity of the clinical picture, the episodes of coma which may occur from time to time in hypopituitarism are caused by different types of functional disturbance. Some patients are suffering from severe hypoglycaemia, others from hypothermia, and a few have a large reduction in sodium and chloride levels, possibly caused by an acute adrenal insufficiency or resulting from the preceding attack of vomiting and diarrhoea. To this list we would add water retention as a possible cause of coma and death.

Case 1 was first diagnosed as suffering from hypopituitarism when she was admitted to hospital in coma as an emergency case. She was not hypoglycaemic, and recovered consciousness during the next three days without

any form of treatment. After the clinical diagnosis had been fully confirmed by numerous investigations (Table I) she was treated with A.C.T.H. at intervals for the next eight months and responded extremely well. On two occasions, however, she developed fairly severe water retention, although the dose of A.C.T.H. which she was receiving at the time was not excessive (40 or 60 mg. daily) and she had previously received similar doses for several weeks without untoward effects. We attributed the attacks of water retention to the small quantities of pitressin which we believed some of the early batches of A.C.T.H. contained, and she recovered on each occasion when the A.C.T.H. was stopped for a few days and then changed to another batch. She was discharged from hospital on a maintenance dose of 25 mg. daily, but unfortunately she left the area in order to make contact with her husband, from whom she had been separated for several years, and we lost sight of her.

She was readmitted five months later suffering from severe hypopituitarism, and went into coma while we were carrying out a further series of investigations and before any form of treatment was started. During the five days preceding death there was a considerable decrease in the urinary volume and in the serum sodium, which fell from 137 to 116 mEq/l. The serum potassium also fell from 4.6 to 2.9 mEq/l. Urinary studies showed that this was due to water retention and not to urinary lose of electrolytes. There was no decrease in haemoglobin or haematocrit levels in the blood. When she was in coma the blood sugar was 65 mg./100 ml. and the rectal temperature dropped to 95° F. (35° C.). She looked bloated, and became more so as the depth of the coma increased. Measures to treat the hypothermia raised the rectal temperature to 99° F. (37.2° C.), and she was given 125 mg. of cortisone intramuscularly on the day before she died.

At necropsy the pituitary gland was found to be considerably reduced in size, weighing 0.21 g., and the thyroid gland, the ovaries, and the uterus were very small. The suprarenals were leaf-like bodies and showed severe atrophy of both cortex and medulla. The atrophy was most noticeable in the cortex, which was reduced to a thickness of some twenty cells. There was marked interstitial oedema in the myocardium, both muscle bundles and individual fibres being separated by free fluid. In the brain the Virchow–Robin spaces were distended with fluid and there was some oedema of the pia arachnoid. There was also moderate interstitial oedema in the medulla of the kidneys though not in the lungs. The pituitary was largely replaced by hyaline and fibrous tissue, only a few groups of parenchymatous cells remaining.

We feel that this case illustrates the danger of the disturbance of water balance that may exist in severe cases of hypopituitarism, and the appropriate treatment would have been to give the patient moderate doses of cortisone before she was moribund. On the other hand, Case 5 drifted into a hypothermic coma while receiving 50 mg. of cortisone daily, and recovered after cortisone was stopped and the body warmed. Recovery might have been more certain if we had also injected sodium thyroxine on the lines attempted by Summers (1953) for the treatment of myxoedema coma. In other cases of hypopituitarism the episodes of coma are caused by severe hypoglycaemia, the most effective treatment for which is the administration of intravenous glucose combined with repeated estimations of the blood sugar.

Our experience of six cases of coma encountered during the past few years, and a study of other reports, have emphasized the diversity of the functional disturbance causing the coma and the need for biochemical investigations to be carried out before treatment is started. The administration of cortisone may save life in some cases, especially when there is evidence of water retention, but in coma associated with hypothermia other measures are likely to prove more successful, and measurement of the rectal temperature, if necessary with a bacteriological thermometer, should be included in the clinical examination.

Summary

The clinical features of nine cases of hypopituitarism and the value of biochemical investigations are discussed.

Treatment with cortisone and thyroid has proved more satisfactory than with A.C.T.H. or cortisone alone. The addition of methyltestosterone is recommended in some cases.

The abnormality of water balance in hypopituitarism is emphasized, and it is suggested that water retention may be one of the causes of coma in this condition.

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OSTEOARTHRITIS AND REST

BY

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Current treatment of osteoarthritis of the weight-bearing joints, if one looks into recent textbooks and articles on the subject, emphasizes the value of rest; rarely are its hazards even mentioned. The patient is encouraged to become slimmer, less active, and to reduce his activities rather than the reverse. The patients themselves have different views in most cases. Fletcher (1951) states: "Most patients are under the impression that they must use their joints as much as possible, and that if they do not they will become crippled." In Hollander's 5th edition of Comroe's *Arthritis* we read, "Many individuals suffering from degenerative joint disease are obsessed with the idea that their joints will become stiff unless they exercise them continuously; this is not true." Substitute the word "periodically" for "continuously" and it is perfectly true. Patients get to know their arthritic joints and learn how to live with them. Their statements should not be lightly discarded or dis-

credited. Buckley (1938) and Fletcher (1948) are careful to point out, though rest for the affected joint is important, invalidism must be avoided, the first author emphasizing the value of exercises to prevent contraction of the capsule of the hip. Steinbrocker *et al.* (1950), in an article entitled "Musculo-skeletal Inadequacy and Failure in the Aged," emphasize that rapid and disabling progression of symptoms may occur even with mild osteoarthritis.

While there is no doubt that overactivity and stresses and strains aggravate the condition there is also no doubt that too little activity does so also. Overexertion and excessive use of an affected joint will produce a sharp reaction within the next 24–48 hours, but immobility may produce a much longer disability. This is a lesson we have learned not from a study of patients in beds for rheumatic sufferers but in the general medical wards, where cardiac decompensation, bronchitis and bronchopneumonia, coronary thrombosis, bleeding peptic ulcers, and other diseases, usually in patients over 60 years of age, cause immobilization in bed for periods of several weeks.

At the end of such a period of bed rest not infrequently an equal period of time is spent in getting the patient on to his or her feet again. Previously complaining little or not at all of osteoarthritic hips or knees, the patient is now severely incapacitated and weeks of rehabilitation are necessary before discharge is possible. This is no small problem; several months of hospital time are taken up each year treating osteoarthritis in patients who were admitted severely ill for some other disorder. With long waiting-lists this is a criticism of our existing methods, and constitutes yet another argument for early mobilization and exercises in bed as soon as the patient's primary condition permits. Even now that we are fully alive to the problem valuable hospital time is spent treating osteoarthritis aggravated by bed rest. The following case histories are unfortunately not uncommon in the general medical wards, do what one can.

Illustrative Cases

Case 1.—A man aged 68 was admitted to hospital on October 13, 1953, with a typical history suggesting myocardial infarction; this diagnosis was confirmed on electrocardiographic examination. Twelve years previously he had had peptic ulceration treated conservatively; mild angina of effort had been present for two years. At no time had he suffered from pain or stiffness of any joint, and his gait was normal. Treatment of the cardiac disease necessitated three and a half weeks' rest in bed, although he was allowed to use a commode after the first week. Two weeks after admission he complained of stiffness and numbness of the right leg, and on examination it was found that he had considerable limitation of movement in his right hip-joint, particularly of abduction. *X*-ray examination at this time revealed gross osteoarthritis of the right hip and slightly of the left also. Leg exercises were started while he was in bed, but when the time came for him to be mobilized he was scarcely able to stand on his right leg. Only after four weeks' perseverance with the aid of physiotherapy was he able to walk without assistance or the use of sticks. He was discharged to convalescence on January 7, 1954, still with a considerable limp.

Case 2.—A Chinese cook aged 69 was admitted on April 24, 1953, with haemoptysis due to pulmonary tuberculosis. This required an initial period of bed rest for three months. On getting out of bed at the end of this time he complained of difficulty in walking and pain in both hips. Examination revealed gross limitation of hip movement. He had previously led a fairly active life negotiating several flights of stairs daily, but had used a stick for two to three years. *X*-ray examination of the hips showed osteoarthritic changes. He was given active physiotherapy, but his discharge from hospital was delayed for four weeks, as he was unable to ascend or descend a flight of stairs until this time.

Case 3.—A woman aged 68 was a known case of diabetes mellitus of four years' duration stabilized on diet alone. She was well and fully mobile until two weeks before admission, when she went to bed at home with an upper respiratory tract infection. This was followed by malaise and vomiting, and two days before admission she fell out of bed and injured her right knee. She was admitted for stabilization of her diabetes on August 15, 1953. On examination she was grossly obese, and an effusion was present in the right knee. On diet alone her diabetes was satisfactorily controlled within a week. The right knee was treated by rest and immobilization with passive movements for one week, and an attempt was then made to mobilize her. On getting out of bed, however, she complained of severe pain and stiffness in both knees, and an *x*-ray film showed gross osteoarthritic changes. She was given active physiotherapy, but required another three weeks in hospital before she was fit to be discharged.

Case 4.—A woman aged 79 was admitted to hospital in a collapsed state with a history of an attack of abdominal pain and vomiting. Her general condition necessitated a period of four weeks' rest in bed. Towards the end of this period she complained of pain and stiffness of the left knee. The latter was slightly swollen, with some fluid in the joint. Movements were painful and limited to about 90 degrees of flexion. *X*-ray examination showed degenerative changes in both knees and hips. She stated that while in hospital two years previously she had had a similar attack which involved both knees, the right one being more affected than the left. She was treated then with heat and exercises, and her condition improved, leaving her with only minor degree of pain and stiffness. On the present occasion heat in the form of a kaolin poultice was applied to her left knee and at the same time her activities were gradually but rapidly increased. She was discharged to convalescence 10 days later, walking well, stiffness and swelling having disappeared, and with minimal pain only.

Comments

While most current textbooks on the subject are careful to recommend only short periods of rest in the treatment of osteoarthritis, few emphasize the real dangers of prolonged immobility. Perkins (1953) states that osteoarthritis has two main pathological features—first, the faulty nutrition of the cartilage, which fibrillates and "wears out"; and, secondly, contraction of the capsule so that the range of movement diminishes. "When a person is trying all the time to move a joint beyond the range allowed by the capsule, the capsule is subjected to repeated stretching. The symptoms of osteoarthritis are in the main caused by the reaction of the capsule to this repeated stretching." Kellgren and Samuel (1950) and others have emphasized the importance of the capsule as a cause of pain; it has an abundant nerve supply, unlike the synovial membrane.

Lloyd-Roberts (1953) considers the development of osteoarthritic changes in a hip-joint to be somewhat as follows: the cartilage, fibrillating, throws off small particles which are engulfed by the synovial membrane, which becomes hyperplastic. Sustained synovial hyperplasia is followed by capsule fibrosis, particularly in the most dependent postero-inferior pocket of the joint. Pain on certain movements is caused by stretching of the capsule, which gradually shortens with increasing fibrosis as the synovial membrane also fibroses. Restriction of movement of the hip causes a smaller area of the femoral head to come into apposition with the acetabulum and aggravates the degenerative changes in the small area of degenerating or degenerated cartilage bearing the body weight. He writes: "It

has already been suggested that shortened and thickened capsule becomes tense prematurely and so restricts the range of hip movement. It is now suggested that if movement continues beyond this limit imposed by the shrunken capsule, and if at the same time body weight is added to the movement, a considerable traction force is likely to fall upon this abnormal ligament, thereby producing pain and protective muscle spasm." He explains the characteristic position of the osteoarthritic hip—adduction, flexion, and lateral rotation—in terms of capsular fibrosis and shortening; this position, at first the painless one, becomes in time the fixed and permanent one.

Harrison *et al.* (1953) made the interesting discovery, in their thorough and painstaking study of the osteoarthritic hip, that the earliest degenerative changes in the cartilage are not in the weight-bearing areas but in the non-weight-bearing areas. They found that daily use preserved rather than wore out articular cartilage, and state "... inadequate use is the commonest cause of cartilage degeneration," and again "... the necessity for use and compression of cartilage in order to maintain its continued health strongly suggests that mechanical forces are concerned with cartilage nutrition."

The above findings all help to explain the deterioration which occurs in a patient's weight-bearing osteoarthritic joints during a period of complete bed rest. In bed the hip tends to be held in flexion and lateral rotation with the knee flexed; therefore a very vigorous policy of routine exercises for all patients confined to bed in the ward is required several times a day.

In orthopaedic wards of military hospitals overseas during the war routine exercises were carried out at set intervals to prevent renal calculus formation, the so-called "kidney drill"; a similar routine is necessary for the elderly bed-fast osteoarthritic patient in civilian medical wards. To prevent deterioration in osteoarthritis of weight-bearing joints certain common-sense measures may be taken. The commode is usually preferable to the bed-pan, and, unless patients must not or cannot be taken from bed, this time out of bed can be used also for exercising hips, knees, and ankles. Elderly osteoarthritic patients should be mobilized as soon as possible—a measure which will also lessen thrombo-embolic complications, and an active programme of exercises in bed should be undertaken from the time they are admitted to the ward if their general condition permits. Patients able to do so can avoid the pitfalls of the flexed hip and knee by lying flat in bed, with pillows and back rests removed, twice a day. Selected patients with deformities already present can be induced to spend equivalent periods in the prone position.

Analgesics should be used freely over such active periods if pain prevents proper co-operation, for effective analgesic "cover" for exercises is invaluable. Phenylbutazone ("butazolidin"), with its prolonged action, would be most useful were it not for its toxic side-effects, the most important in this group of patients being gastric irritation and salt retention with resulting oedema and precipitation of congestive cardiac failure; in certain carefully selected patients, nevertheless, it may prove very useful. Intra-articular hydrocortisone may be used in cases in which the knee is at fault; unfortunately, injections into the hip are far less effective (Hollander, 1953) and much more difficult. An injection into the knee of 25–35 mg. will often help in rehabilitation, and Hollander *et al.* (1951) found the results better in osteoarthritis than in rheumatoid arthritis, as the effects appeared to last longer. Injection of a local analgesic into ligamentous attachments is useful in mobilizing stiff and painful knees. None of these measures may be possible in severely ill patients, but emphasis should be on as early mobilization as is possible compatible with their medical condition. This has been emphasized by many writers in the past—for example, Asher (1947) in an article entitled "The Dangers of Going to Bed"—but we feel that the subject needs even further emphasis in this ageing community.

Summary

While graded rest is quite correctly the basis of orthodox treatment of osteoarthritis of the weight-bearing joints, there has been too little emphasis in the past on the dangers of immobility and excessive rest in this disease. Aged patients admitted into the general wards of our hospitals are not infrequently severely disabled by aggravation of their pre-existing osteoarthritis by complete bed rest. Attention is drawn to this problem and certain therapeutic measures are suggested.

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NEPHRECTOMY IN HYPERTENSION DUE TO RENAL ARTERY INFARCTION

WITH SUPERINFECTION OF STREPTOCOCCAL ENDOCARDITIS BY FUNGUS

BY

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Of 46 cases of hypertension due to unilateral renal disease and cured by nephrectomy, Langley and Platt (1947) found renal artery infarction recorded as the cause in one only. A similar case, observed before hypertension developed and for three years after great relief by nephrectomy, is here described. It seems also to be one of the earliest recognized cases of fungous endocarditis in Britain. No record has been traced in this country, and very few elsewhere, in which this infection complicated bacterial endocarditis.

Case Report

A single girl aged 17 was admitted to Brighton General Hospital on June 21, 1950, with a six-weeks history of joint pains and fever which resisted salicylates and "cremomerazine." Past history: a weak heart diagnosed aged 8, but no previous rheumatic disease. Family history: non-contributory. No epilepsy. Clinical examination: T. 101° F. (38.3° C.). Synovitis of small joints of right foot only. Heart: not enlarged; systolic murmur maximal midway between apex and lower sternum; B.P. 120/80. Urine normal. Blood: Hb, 60%; red cells, 3,510,000; white cells, 7,700 (normal differential); E.S.R. 63 mm. in first hour; haematocrit 28%, adjusted 32 mm. Nose swab: *Staph. albus* and scanty *Staph. aureus*. Throat swab: no growth. *X*-ray examination: heart, lung, and vascular shadows physiological. E.C.G.: P–R interval 0.24 second. Treatment with salicylates to the limit of tolerance did not reduce the fever.

July 2: B.P. 120/80. Urine: many red cells with granular and epithelial casts, albumin 0.07 g. per 100 ml., and sterile culture. Retinoscopy: superficial haemorrhages in both fundi and blurring of right disk. July 4 and 5: blood

cultures, *Str. viridans*, sensitive to penicillin. July 6: soluble penicillin, 500,000 units six-hourly, begun. Relief incomplete. July 17: T. 102° F. (38.9° C.). Pain in right thigh and left foot, subconjunctival haemorrhages in both eyes, a small haemorrhage in right fundus, petechiae in neck and front of chest, axillae, and abdomen. B.P. 135/85. Spleen palpable. Blood urea 32 mg. per 100 ml. Urine: red cells, casts, and sterile culture. July 18: blood culture sterile. Penicillin continued and aureomycin, 100 mg., given for one dose intravenously, followed by 500 mg. orally four times daily for six weeks. Response was still slight and slow, fever, subcutaneous purpura, and joint swelling persisting, with, on August 15, photophobia and left head pain. During the next week, however, fever, purpura, and joint pains disappeared. On August 23, aureomycin was omitted, but penicillin was continued until October 19. The remission lasted only from August 23 to 30, when pain and tenderness appeared in the left loin and hypochondrium, not very severe, lasting 12 hours. T. 104° F. (40° C.). Urine: albuminuria, no gross blood. Splenic infarction was incorrectly diagnosed.

For a fortnight there was apparent improvement, with no tenderness or fever, but albuminuria 0.2 g. per 100 ml. No record of the blood pressure was made. On September 18 blood pressure was 200/140 in the morning. Retinae: exudates and haemorrhages. Urine: many red cells, a few white cells and hyaline and epithelial casts, and albuminuria 0.2 g. per 100 ml. In the afternoon vomiting and in the evening status epilepticus developed, needing thiopentone, 0.25 g., intravenously for control. Cerebrospinal fluid: white cells less than 1 per c.mm.; protein 30 mg. per ml. September 19: semi-comatose, mild right hemiplegia and aphasia, plantar reflexes flexor. Blood: white cells, 23,000 (polymorphs 87%). Blood urea, 38 mg. per 100 ml. September 20: conscious, and retrograde amnesia for preceding months; severe headache; B.P. 190/160. For the next fortnight intermittent unconsciousness, convulsions, fretfulness, whining, and vomiting continued, with brief intervals of improvement. Urine: many red cells and albumin 0.24 g. per 100 ml. Hypertension increased to 210/170 by October 19, with vomiting and petechial haemorrhages, and hypotensive treatment was begun (hexamethonium iodide to 100 mg. intravenously four-hourly) for four days until urinary retention and faecal impaction appeared, with the blood pressure 100/80. Oral administration was substituted and symptomatic relief obtained, though hypertension persisted (180/140). Urinary infection with *Bact. coli* was treated by streptomycin, and by November 21 the urine was sterile, with few red and white cells, occasional hyaline and epithelial casts, and albuminuria.

On November 28 renal investigation was at last begun. Intravenous pyelography showed secretion from right kidney but none from left. Urea clearance (blood urea 17 mg. per 100 ml.) 19% in first hour (103 ml.), 35% in second hour (193 ml.). Cystoscopy: normal bladder and ureteric orifices. Indigo-carmine injection: no excretion from left, good concentration in four minutes from right: urine from right kidney, few red and white cells, no casts or crystals, sterile, albumin 0.2 g. per 100 ml. Retrograde pyelography on left: normal renal pelvis. December 15: left nephrectomy (Mr. Keith Powell); removal of infarcted kidney and biopsy of left adrenal gland. B.P. pre-operatively 200/150; fell immediately after operation to 130/70; rose to 180/110 in the evening; remained during the next week 130/90, the maximum reading on discharge a month later being 140/105. On April 23, 1951, it was 150/95 and the patient resumed work (wood sorting). On March 31, 1952, B.P. was 130/90, and on March 16, 1953, 125/95. She had had psychological difficulties, being one of a "problem family," and, though she complained of fainting attacks at menstrual periods, was thought to be restored to the degree of physical and mental activity that would have been expected without her illness. She then married, and it appeared that her attacks were epileptiform.

She was readmitted to hospital on December 31, 1953. Blood pressure on admission, 135/95. Clinically, condition unchanged. The day after admission she became inaccessible, rambling, tearful, and unable to remember her address. While her blood pressure was being taken (170/135) a major epileptic fit developed, with deviation of head to the right. On recovery, B.P. fell to 135/95 and continued between 135/90 and 160/100 during her stay, the higher readings being associated with emotional tension.

Investigations.—W.R., negative. Urine: sterile, with occasional red and white cells (catheter specimen); no albumin or casts. Dilution to S.G. 1002, concentration to S.G. 1020. Blood urea 30 mg. per 100 ml. Urea clearance 30% (40 ml. possible error in collection) and 80% (115 ml.). Urea concentration 2.2 g. per 100 ml. and 3 g. per 100 ml. Serum proteins, blood count, and E.S.R. physiological. Heart condition (Dr. Kemball Price): ventricular septal defect or mitral incompetence. Electroencephalogram: the alpha rhythm not very stable, showing a frequency of 10–11 c./sec. It is better seen on the right side. There is a great deal of medium voltage, 4–6 c./sec. activity, and sharp waves having a tendency to occur in paroxysms. . The slow waves occur in all leads, perhaps more on the left side. The paroxysmal sharp waves occur bilaterally, but are of highest voltage over the left fronto-temporal area. Over-breathing increases the number of paroxysms and enhances the asymmetry slightly. Flicker did not add useful information. This record suggests a diffuse degenerative lesion affecting the whole brain, with maximal damage in the left fronto-temporal area. The lesion is epileptogenic (S. Kay, January 16, 1954).

During her stay in hospital the B.P. varied between 135/90 and 160/100: it was labile and the higher readings were associated with considerable emotional tension. She was discharged on routine treatment for epilepsy, and on February 22 reported one very mild attack.

Pathological Report

A specimen of the adrenal gland showed no definite abnormality (R. W. M. Johnson). The pathological report (Professor A. C. P. Campbell) was as follows:

"The kidney is considerably shrunken, weighing 70 g. The capsule has been stripped. The surface is pitted with coarse depressed scars, some of them brown-pigmented, and between the scars there is slight, fine granularity. The colour shows a patchy alteration of congestion and pallor.

"On dissection the renal artery at the point of resection just outside the hilum is shrunken and occluded by organized thrombosis. As the artery is traced into the hilum it becomes lost in a fibrous granuloma about 15 mm. in diameter, of pale-grey colour flecked with iron pigmentation. Similar smaller granulomata are seen in the hilum apparently on the course of the lobar branches of the renal artery. The kidney tissue is markedly pale (the specimen has apparently been a considerable time in formalin) and cortical pattern and cortico-medullary distinction are grossly blurred. The pelvis and calices are contracted; their mucosa appears normal.

Microscopical Examination

"Sections of the kidney show a uniform tubular atrophy of considerable degree throughout with a little diffuse fibrosis and considerable interstitial lymphocytic infiltration. The depressed scars noted above show a more complete atrophy and fibrosis indicative of areas of complete infarction. The generalized partial atrophy is compatible with partial infarction from a not quite complete ischaemia.

"The granuloma on the course of the renal artery shows an interesting picture. Segmental fragments of the artery and of its primary branches can be seen persisting within it. The granuloma is of tuberculoid type, showing small central micro-abscesses full of polymorphs, each surrounded by a zone of endothelioid cells and occasional Langhans's giant cells, outside which there is profuse lymphocyte and plasma-cell infiltration and extensive fibrosis. Within some of the abscesses there are collections of granular material partly

eosinophil and partly so basophil as to indicate calcification (confirmed by von Kossa's stain). These structures have the appearance of fungal colonies. They show a mixture of rather irregular rounded granular bodies with occasional mycelial strands. Some of the colonies show at the periphery a distinct margin of scalloped clubbing suggesting a radiate structure in the colony. The colonies are mainly Gram-negative, but some granules are Gram-positive. Possibly the negative Gram stain is due to degeneration; the irregular morphology of the individual bodies and the calcification indicate that the organism is in a degenerative state. It is unfortunately not possible to identify the fungus more exactly because of these degenerative changes.

"Throughout the substance of the kidney, mainly in the cortex, there are occasional microscopic granulomata of exactly similar structure. These do not appear to be necessarily related to arterial branches.

"The atrophy of the kidney is compatible with ischaemia produced by embolic blocking of the main renal artery. The fact that the atrophy so produced is in many places only partial could be explained by some degree of blood inflow through the capsular circulation and possibly via small accessory arteries. Histologically, the nature of the granuloma on the course of the renal artery and of those in the kidney substance is, I think, quite incompatible with a *Str. viridans* infection. One must, I think, conclude that there has been a fungous endocarditis with embolization of the renal artery by an infected vegetation. Whether the fungous infection was combined with a *Str. viridans* infection or whether the positive viridans blood cultures are a red herring I do not know.

"Endocarditis due to fungi of various sorts has been reported—for example, from monilia, erysipelothrix, leptothrix, histoplasmosis, sporotrichosis, blastomycosis, actinomycosis. The histology of the inflammatory reaction does not suggest actinomycosis, but could be compatible with several of the others."

Comment

Three points of interest are the relation of acute rheumatic manifestations to infection with *Str. viridans* or fungous infection, that of hypertension to the renal lesion, and the part played by the fungous infection.

Infective endocarditis preceded by acute rheumatism is recognized by clinicians (Friedberg, 1950), as is the occurrence in it of acute rheumatic cardiac disease by morbid histologists (MacIlwaine, 1947). The present view of pathologists is probably that the viridans infection establishes itself more easily because of rheumatic damage to tissues or disturbance of defence mechanisms, or both.

Hypertension related to human unilateral renal vascular disease has rarely been proved, the common lesion being pyelonephritis (Goldblatt, 1949; Pickering and Heptinstall, 1953). Extensive general surveys of cases showing renal infarction (Barney and Mintz, 1933; White and Porter, 1941; Hoxie and Coggin, 1940; Ormond, 1948) do not mention hypertension. Oppenheimer *et al.* (1939) found after 5,000 post-mortem examinations of hypertensive patients that though the pressure had been higher when one renal artery was notably damaged it was very difficult to bring evidence from observations on man on the incidence of hypertension. Cases which show hypertension due to renal vascular disease clearly relieved by nephrectomy are reported by Boyd and Lewis (1938), Leadbetter and Burkland (1938), Howard *et al.* (1940), Shea *et al.* (1948), Cornwell (1949), Owen and Pearlman (1951). The experiments of Goldblatt (1937) showed that in his experimental animals complete obstruction of the main renal vessel did not produce hypertension. In the present case renal artery obstruction was followed by only patchy atrophy, presumably due to partial ischaemia. Capsular and accessory vessels can, Professor Campbell suggests, provide considerable blood supply. In some patients with completely occluded renal vessels this would correspond to that provided by the partially occluded vessels necessary for hypertension in Goldblatt's experiments.

The unexpected finding of a granulomatous process in the removed kidney related to masses of fungus caused careful review of the case records. There is no doubt that blood culture on separate days grew a penicillin-sensitive streptococcus. Response to penicillin was, however, unsatisfactory, though further blood culture grew no bacteria. After aureomycin had been given as well for three weeks the fever was, in general, controlled, but occasional embolic signs occurred. The unusually severe symptoms and persistent fever in a penicillin-sensitive bacterial infection were probably evidence of an added fungous endocarditis.

Fungous endocarditis has been reported, mainly from the United States, twenty references (none from this country) being found between 1939 and 1952. A frequent cause is drug addiction, with intravenous administration (Pasternack, 1942), but such endocarditis has developed under antibiotic treatment of other infections (Cassels and Steiner, 1944; Geiger *et al.*, 1946; Zimmerman, 1950; Kunstadter *et al.*, 1952). Geiger and others report endocarditis with combined bacterial and fungous infection but with death. In the present case the long period of observation makes it seem that the unidentified fungous endocarditis was cured.

Summary

A case is reported of hypertension in a normotensive patient with infective endocarditis developing in the course of rheumatic fever, due to renal artery infarction and relieved for four years by nephrectomy. The infecting organisms were *Streptococcus viridans* and an unidentified fungus.

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"Many unmarried mothers do not know that they can adopt their own children," writes the General Secretary of the National Council for the Unmarried Mother and her Child in the July issue of *Marriage Guidance*. The procedure is the same as in adoption by a childless couple, and there is a probationary period before the adoption is ratified. This procedure has several advantages for the unmarried mother and for her child. There is no need to pose as "Mrs.," with the attendant difficulties when seeking work or making claims for dependants' tax relief or other legitimate and often much-needed financial help. The adoption certificate establishes the mother as her child's legal guardian in a way which needs no further clarification and is easier to explain to the world. The writer goes on to point out that it is wise for a mother who has taken this step, when questions are asked by the child, to be frank about the real relationship, and as time goes on to make it clear why the adoption was made.

ORGANIC SYNDROMES PRESENTING AS INVOLUTIONAL MELANCHOLIA

BY

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The "involutional period" may be defined as a physiological epoch which occurs in both men and women and is manifested by various mental and physical changes, some trivial and others of much importance. During this epoch, which roughly may be said to be between 40 and 55 years in women, and between 50 and 65 in men, the syndrome of "agitated depression" often arises, and, although seen more frequently in certain ethnic groups (for example, the Scots and Irish), it occurs often enough elsewhere to be readily recognizable, not least by its excellent response to electroplexy.

When Kraepelin in 1896 first made the important differentiation between the manic-depressive psychosis and dementia praecox, he kept cases of depression occurring at the involutional period separate and gave to these the name of melancholia. Since that time this subject has been the occasion of much discussion. Many psychiatrists, for example, have considered that the affective disturbance should be looked upon as a modified manic-depressive psychosis, occurring at a particular time and age. Other workers (Palmer and Sherman, 1938), accepting the condition as an entity, found constant premorbid personality trends of obsessional characteristics and hyperreligious ideas. Gillespie (1929), in differentiating types of depression, stated that there was a distinct involutional group whose chief characteristic was preoccupation of a hypochondriacal type.

Henderson and Gillespie (1950) believed categorically that the concept of involutional depression *per se* is fully justified. They considered that certain features are characteristic of the syndrome, such as agitation, depression, anxiety, feelings of unreality, and hypochondriacal self-concern. Such symptoms, arising in a person with no history of previous depressive illness and with a premorbid personality of the rigid obsessional type during the period of the climacteric, are regarded as diagnostic of this particular type of illness. Muncie (1948), from a psycho-biological point of view, classifies under holergasias (psychoses), five major groups of depression, one of which he terms involutional on its own.

In general, most of the literature agrees with this concept, emphasis being placed in one view upon the endocrine changes (Hemphill and Reiss, 1940), in another upon the dynamic psychological changes (MacCurdy, 1925), while yet others feel that all these factors play a composite aetiological part (Nielson and Thompson, 1947).

The purpose of this paper is to bring together four cases, all of which presented clinically as an involutional type of depression, and in all of which was found, on subsequent investigation, evidence of various organic illnesses, the significance of which—in this setting—is discussed later.

Case 1

A man aged 56 was admitted in an acutely disturbed state to hospital in June, 1951. During the previous nine to twelve months he had been complaining of general debility, depression, and being "unable to take any interest in anything." He was happily married, and had two sons, both well. He had no domestic or financial worry, nor was there any history of psychological illness in his family. A teetotaller and non-smoker, he derived a great deal of satisfaction out of his garden. Up to the day he was seen he had been driving a corporation bus, a job which he had held down for many years. According to his wife, he had always been a hard worker, conscientious, and very particular about his job and his personal appearance; he was mainly interested in his home and garden, and had never missed a day's work before.

Clinically, he was moderately depressed and inclined to cry during the interview. His agitation was great, and he presented a picture of extreme anxiety. His talk was reasonably spontaneous, but was preoccupied with ideas of "low-spiritedness" and pains in the head, back, and legs. He was very concerned that he might be putting his passengers' lives in danger by continuing to drive. He also complained of insomnia, "waking up full of fears about three o'clock and unable to go off again." There was no delusional or hallucinatory ideas, and he was correctly orientated in all spheres. His memory for remote events was good, but rather poor for recent and retention material. It was thought at the time that this was probably due to preoccupation with his own depressive ideas.

Physical examination at that time did not add very materially to a diagnosis of involutional depression. In hospital the usual investigations (*x*-ray examination of the chest and skull, blood Wassermann reaction, and urine analysis) were all negative, but several electroencephalographic reports suggested an abnormal tracing of an organic type in the left hemisphere, around the Sylvian point. At the same time, ten days after admission, he began to complain of weakness in his right arm and leg. This could be demonstrated, and a condition of slight blurring of the left disk margin was noted at this time. No abnormal manometric results were found on lumbar puncture, but there was 100 mg. of protein per 100 ml., with a triple increase of globulin. A few days later a bilateral carotid arteriography showed an outline of a large vascular tumour, suggesting a meningioma, in the left post-frontal parasagittal region. Operation was carried out on July 16, and a meningeal tumour weighing 60.8 g. was removed. Post-operative convalescence was uneventful, except for an epileptic attack a month later. Because of this he was given prophylactic phenobarbitone, and there has been no recurrence one year later. Since the operation there have been no periods of depression or agitation, and his family maintain that, apart from residual weakness of the right arm and leg, he is his "old self" again.

Case 2

A married woman aged 43 presented initially as a psychiatric problem, although clinical neurological examination a few days later clearly revealed signs of a cerebellar disorder. She had apparently awakened one morning at her usual time, got out of bed, and then suddenly experienced a severe attack of giddiness with nausea and vomiting. Later that day she became acutely depressed and agitated, and when her doctor saw her she presented as an acutely anxious, tearful, and very dejected patient. Her thought content was predominantly morbid, with many feelings of guilt and hypochondriacal ideas. This mental state—typical of that seen in the classical involutional melancholia—continued for about three months, and then resolved as suddenly as it had begun, when the neurological symptoms and signs described below were resolving.

On admission to a psychiatric hospital six days after the onset of her illness, as a case of "acute agitated depression," she presented nystagmoid movements of both eyes, dysphagia, and dysarthria of staccato type. There was loss of power and reduced tone in the right arm, and to a slighter extent in the right leg. Gross intention tremor, ataxia, and rebound phenomena were also observed in the right arm. Over the whole of the left arm and leg there was a patchy hypalgesia. The C.S.F. was not under pressure.

but 92 lymphocytes per c.mm. were found, together with increased protein (80 mg. per 100 ml.) and a triple-positive globulin. The Lange reaction was negative, as was also the W.R., and chlorides and sugar were within normal limits. *X*-ray films of the chest and skull were normal and a blood count showed no abnormality. Blood W.R. was negative.

Clinically, the condition suggested a cerebellar apoplexy, the underlying pathology of the nature of a thrombosis of the posterior inferior cerebellar artery. No further elucidation was ever made, and over the next three months the C.S.F. slowly resolved to normal. During this time four examinations of the fluid showed a reasonably close correlation between the progressive normality of the fluid and the diminution of the anxious and depressed clinical state.

This patient had no previous history of illness of any sort. A paternal aunt had been in a mental hospital for many years, suffering from "melancholia." She had three children, aged 19, 15, and 8, all well. Her menses had become irregular about seven months before the onset of the illness, and she had complained of some "flushings" and headaches. She was a rather quiet, rigid, seclusive woman, who took a great pride in her house and personal appearance. She had no outside interests and her husband maintained that her illness was really due to "her serious nature and her inability to relax and enjoy herself." Although the precise pathological process was not elucidated in this case, and may have been associated with a virus meningo-vascular infection, it seems to be a reasonable example of the type of depression under consideration, being associated with an acute neurological disorder in a person whose basic personality is usually equated with an involutional type of anxious depression. The affective reaction began suddenly, and three months later resolved, *pari passu* with the initial clearing-up of the dysphagia, dysarthria, and ataxia.

Case 3

A married woman aged 53 was referred for hospital treatment as a case of early involutional melancholia, although it was noted at the time that her blood picture was "probably of aetiological importance." Her menses in the past year had become rather irregular and scanty, and for the past two months she had complained of headaches, acroparaesthesia, and flushings of head and neck. In addition to these symptoms she was noted to have become very depressed, with bouts of crying, during which she would moan and maintain that her whole life was nearly finished and "everything was hopeless." Objectively, she showed much anxious preoccupation with her bodily discomforts and at times gave way to actual panic attacks of screaming, believing she was about to die. She had some feelings of unreality and ideas of reference, believing that her neighbours were constantly discussing her. Apart from her depressive thought content, she showed many ideas of guilt in relation to her younger days as a barmaid, when, she maintained, she was one of the most wicked women in town.

There had been no previous psychological illness, but some years ago her doctor had treated her for anaemia with liver injections. These had been stopped eighteen months before, as she had "come to the end of her course." She had no family history of any relevant importance, and her husband described her as "easily upset, a martinet about tidiness in the house, very fussy, and capable." Her aged father maintained that she had been a chronic worrier from childhood.

Clinical examination revealed a generalized icteric tinge and mild glossitis, and it was noted at the time that there was considerable oral eructation. Nothing else was made out on examination. There were no demonstrable neurological signs. Blood examination showed: red cells, 1,480,000 per c.mm.; white cells, 4,640 per c.mm.; haemoglobin, 37%; M.C.V., 108 μ^3; M.C.H.C., 36.9%. The differential white count was proportionately normal. The film showed marked anisocytosis, polychromasia, and a few megaloblasts. Reticulocytes were 0.8%. A fractional test meal demonstrated gastric achylia. *X*-ray examination of the chest, blood W.R., and urine analysis were all negative, apart from the last, in which there was an increased urobilin.

From these findings a diagnosis of a megalocytic anaemia of the Addisonian type was made and liver therapy was instituted. During the next week or so there was a good reticulocyte response, at its peak going up to 31%. Over the next two months the blood picture slowly improved to normality, and associated with this improvement was lessening of the depression and agitation, although there were fluctuations. At one stage, for example, when her haemoglobin was 63%, she became very paranoid, noisy, and abusive towards the staff, and talked in a conspiratorial fashion about the staff trying to poison her. This may have been due to a fortuitously occurring streptococcal cystitis which appeared then. She was finally discharged with no evidence of agitation or depression, but still rather emotionally labile, with her haemoglobin in the region of 96%.

Clinically this was a case of involutional depression, and the most that could be said at the beginning was that there was an associated anaemia, probably of an Addisonian type. No other treatment except that of haematinics was given, and it was quite clear that the mental state tended to resolve *pari passu* with the improvement in the blood condition. It is assumed that the paranoid outburst during the course of treatment was a toxic-infective process in the form of the cystitis, and the prompt treatment of this quickly cleared up the rather difficult nursing problem which had arisen.

Case 4

A man aged 58 was admitted to hospital in a state of extreme agitation, with a history of depression and agitation for about two months. He could give no coherent account of his illness, and his talk, which was rarely spontaneous, seemed preoccupied with ideas of worthlessness and hopelessness, and a fixed belief that he would be taken to Russia "for punishment."

He was one of nine children, seven of whom were living and well. One of his sisters had had a depressive illness during the puerperium of the first of her children. The patient had two grown-up children, both in excellent health, but he and his wife had had at least four stillborn children. Most of his life had been spent on the railways, mainly as a driver. He had a personality, according to his children, of moroseness, seclusiveness, and rigidity. He constantly worried about his own and their affairs. He would become irritable if slippers or paper were not laid out in their usual positions each night. He was opinionated and intolerant. Frequently he had "beaten up" his wife. As soon as these phases wore off, he would become ashamed and contrite, and buy her several presents to make up for his misdeeds. The patient's daughter was in no doubt that her father's illness was due to "overwhelming guilt about his intolerance."

After admission there was no change in this gross picture of anxious, agitated depression, punctuated by bouts of crying and expressions of misery and hopelessness. Neurologically there were no anomalies, apart from the gross generalized tremor and a slight wasting of muscles around the left shoulder-joint (old injury). So far as his state of general agitation and preoccupation permitted, psychological testing did reveal impairment of memory, especially for recent events and retention, but it was found impossible to apply to him planned performance or abstraction tests. His B.P., blood W.R., electrocardiogram, and *x*-ray films of the skull and chest did not materially add to the clinical conception, which undoubtedly was a characteristic picture of involutional depression.

Ten days after admission, quite suddenly, he had a series of general epileptiform attacks, which were eventually

controlled by intramuscular paraldehyde and phenobarbitone, leaving a right-sided Todd's paralysis which lasted for twenty-four hours. Over the next week these fits continued, but each series was fairly easily controlled. At the time lumbar puncture revealed nothing of significance, either manometrically or on analysis of the fluid. There was no B.P. increase, and the blood urea was twice found to be normal. A blood count likewise was within normal limits. Serial electroencephalograms suggested diffuse organic change, but no localization. A week later an air encephalogram revealed a considerable degree of atrophy of the frontal and right temporal lobes.

Over the next two to three months the picture of anxiety and agitation slowly resolved, and three months after admission more precise psychological testing showed average verbal intelligence but gross impairment of performance ability. Verbal abstraction appeared to be reasonable, but there was a failure in the type of abstraction involving spatial organization and associated performance. There was also gross but selective memory deficits, especially of recent memory.

Eighteen months later he had continued to deteriorate, presenting a picture of almost depressive stupor, lying in bed, incontinent of urine and faeces, and oblivious of his surroundings, taking no interest in any nursing attention, and usually indifferent to questionings. On the rare occasions on which he spoke, his thought content was profoundly depressed, with many suicidal ideas. It is to be noted that over the previous year he had had several courses of electroplexy, with only slight and temporary improvement in his affective state. The diagnosis was a pre-senile dementing condition. The first week in hospital, however, with the history of onset and the clinical picture, particularly the feelings of guilt and remorse, suggested very strongly an involutional type depression. It was the onset of the epileptic convulsions that first persuaded us to look further afield for the pathology and undoubtedly anticipated "naturally" the projected use of electroplexy in the early stages of this condition.

Discussion

It is by no means intended to give the impression that a depressive symptom-complex is not often seen with associated organic illnesses. Kraepelin (1913), for example, was convinced that a disorder of metabolism was usually associated with manic-depressive illnesses, and he enumerates many physical findings, such as infantilism and hydrocephalus, which he felt were intimately connected with the psychiatric manifestations. Depressive manifestations are also well known in the symptomatology of G.P.I., cerebral arteriosclerosis, tumours, and many other diverse conditions. McMenemey (1941) considered that depression is a more characteristic affective state in pre-senile dementias than is excitement. Spillane (1947) mentioned depressive features occurring in various types of nutritional deficiency, especially pellagra.

This paper, however, is concerned with a special type of depression occurring at a physiological epoch and showing in all the patients the particular obsessional type of personality which is so characteristic of this illness. The pre-morbid personality of the usual rigid and scrupulous type, often with an associated tendency to worry unduly, was seen in all of them. The depression when it arose was of the anxious, agitated type, again typical of the illness under discussion.

In Case 1 the relationship between the underlying organic illness and the depression was noteworthy. Sachs (1950) described eight cases of meningiomata presenting as dementia; all of these were clearly so, but it is noted that in Case 8, Miss H. L. presented with depression and had become querulous, hypochondriacal, and aggressive before the more overt signs of dementia had become manifest. Her age, 69 years, alone would have removed her from the group described above, at least from the purist point of view, and, although there is not much information about her pre-morbid personality, it is interesting that in her case a meningioma over the right parietal region of the brain should have produced similar suggestive symptoms in the early states. McIntyre and McIntyre (1942), in a paper on seven cases of brain tumour, reported four cases of meningioma presenting primarily as psychiatric problems; these cases were incorrectly diagnosed as chronic alcoholism, psychosis with Parkinson's disease, arteriosclerotic dementia, and Alzheimer's disease. These authors believe that the meningioma is the "most common tumour producing mental symptoms."

Case 2 might certainly have been diagnosed as a case of cerebellar apoplexy much earlier than it eventually was, but the fact remains that the case presented to her doctor and to her family as one of an acute and agitated depression. On questioning her husband later, he maintained that on no occasion did she complain, after the initial disturbance of giddiness and nausea, of any somatic symptoms or difficulties whatsoever. Her age, menstrual irregularities, and her previous personality all appeared "set" for an early involutional depressive illness.

The same postulates apply to Case 3, although here again there were undoubted physical findings, and the pallor of the mucous membranes and generalized icteric tinge certainly suggested a chronic Addisonian type of anaemia. Osgood (1935) discussed the problem of psychiatric symptomatology occurring in the course of pernicious anaemia, and came to the conclusion that such a relationship was largely coincidental. Many other investigators (Cabot, quoted by Rogers, 1915; McAlpine, 1929; Herman *et al.*, 1937) firmly believed that such a relationship exists. According to Herman *et al.* there are four reasonably common pictures, consisting of—in order of frequency—an acute confusional state, paranoid reaction, affective reaction, and an organic deterioration type. Case 3 showed a typical involutional depression, with the characteristic personality; a megalocytic anaemia which responded well to liver; and a resolution of her mental symptoms, apart from one paranoid outburst which lasted a few days, reasonably parallel to her physical improvement. It would seem to be too much to regard such a relationship as fortuitous only.

Stengel (1943) pointed out how pre-senile dementia may present as an involutional agitated type of illness and how, for example, the apprehension and tension so conspicuous in many cases of Alzheimer's disease recall the characteristic state in involutional melancholia; and he goes on to postulate the idea of a more than superficial relationship between Alzheimer's disease and the deteriorating type of involutional depression. Hemphill and Stengel (1941), in a study of a case of pre-senile dementia, found that the only symptom for a long time was the affective one of depression. Noyes (1947) and Ewen (1947) pointed out the many difficulties of a differential diagnosis between involutional melancholia and cerebral arteriosclerosis. The memory loss, focal neurological symptoms and signs, epileptiform attacks and vertigo, etc., should, of course, be of importance in the differentiation, but in Case 4 there was no such evidence until a week after admission, when indeed the question of electroplexy was being considered.

These four cases, admittedly few in number, do seem to bear out the modern conception of the production of involutional symptoms—that is, that although there are, of course, the regressive glandular change and accompanying psychological changes, these endocrine changes constitute only one factor. Neilson and Thompson (1947) believe that the symptoms "depend partly upon the distortion of previously existing personality defects," and they go on to postulate factors important in the aetiology of the condition—heredity, diminution in activity of endocrine glands, prepsychotic personality, age, and a "realization of instinct decline"—as predisposing factors, and suggest that precipitating factors may be psychic, physical, or both. This conception seems to be a very reasonable one, and with this background the above four cases could be seen in this light; that is, that the organic conditions merely acted as

precipitating causes on a soil already prepared. Put in another way, the affective manifestation of anxiety and depression might seem to be some sort of preformed cerebral function occurring in the personality type and potentially manifesting itself when the right precipitating factor came along.

Malamud *et al.* (1941) take a similar view, and feel that in the "development of the psychoses the pre-morbid personality and catastrophic occurrences before the onset of the illness are of outstanding importance."

From a purely practical point of view, exhaustive evaluation of any physical anomalies seen in association with this type of illness, even if, as in these cases, the whole background seems to be characteristic of involutional depression, is clearly of the utmost importance.

Summary

Four cases of agitated depression are noted, all of which were associated with organic disease.

The depression, its symptoms, signs, and time of occurrence, together with the pre-morbid personality of the patient, were characteristic of the involutional type of illness.

The significance of this association is discussed.

I am grateful to Dr. R. E. Hemphill for permission to publish these cases and to Dr. K. R. L. Hall for his detailed psychological reports.

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A letter in *Science* (June 25, p. 914) records the results of a six-year investigation showing an unexpected correlation between susceptibility to poliomyelitis and genetic traits indicated by pigmentation of the skin, hair, and eyes. The writer, WALLACE L. MINTO, of New Jersey, U.S.A., says that of 1,183 poliomyelitis cases investigated, 1 only had blond hair, blue eyes, and fair skin, 17 had blond hair and brown eyes, while the remaining 1,165 had brown or black hair and eyes. All the fair patients had light attacks of the disease, only two of them having any permanent disability. The observations were limited to members of the Caucasian race. "Obviously, these observed ratios differ significantly from the occurrence of light pigmentation in the general population." The writer then goes on to make a plea that "this variation of susceptibility to poliomyelitis should be taken into account in any statistical study of the value of prophylactic measures"—that is, light- and dark-haired people should be equally distributed in the control and experimental groups.

INCOAGULABILITY OF BLOOD AFTER ACCIDENTAL HAEMORRHAGE

BY

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Of recent years there have been several reports concerning the phenomenon of incoagulability of the blood which sometimes follows accidental haemorrhage (Dieckmann, 1936; Moloney *et al.*, 1949; Weiner *et al.*, 1950; Goodfriend *et al.*, 1953; Stevenson *et al.*, 1953; and Weiner *et al.*, 1953). This blood incoagulability may give rise to severe post-partum haemorrhage, or to uncontrollable bleeding from the wound or even from suture points after caesarean section, and may be so severe as to cause death. It is sometimes associated with spontaneous haemorrhages in various parts of the body.

In spite of the obvious importance of this complication of accidental haemorrhage, and the need for the early recognition and correction of the condition, little or no attention has been paid to it in the British literature.

Case Report

A 10-para aged 40 had had nine previous normal confinements. She was not attending the antenatal department and was first admitted on March 6, 1953, 26 weeks pregnant and giving a history of slight vaginal bleeding for the past four days.

Examination revealed a uterus corresponding in size to the period of gestation. The cervix was normal and closed. The blood pressure was 125/70 and there was no albumin in the urine. Bleeding ceased and the patient was discharged home on March 11.

She was readmitted to hospital on April 3, giving a history of further slight vaginal bleeding. Liquor was draining at the time of readmission, but she was not in labour and a foetal heart could be heard. The pregnancy had now reached 30 weeks, but the uterus was much larger than the dates would suggest. A haemoglobin estimation gave a reading of 5.1 g. per 100 ml. The blood pressure was normal and there was no albumin in the urine. Blood-stained liquor continued to drain and definite labour pains began at 6 p.m. on April 7. Very slight pains continued and no anxiety was felt regarding her condition. At 3.50 a.m. on April 8 the patient had a typical eclamptic fit immediately following a two-hours sleep. The fit displayed tonic and clonic phases and was followed by a coma. The tongue was bitten. Urine showed a faint trace of albumin and the blood pressure was 110/90. Half an hour after the occurrence of the fit bulging membranes were visible at the vulva. These were ruptured and, using forceps, a small dead-born foetus, just over 3 lb. (1.4 kg.) was lifted out of the vagina. A completely separated placenta immediately came away after the delivery, with 10 oz. (285 ml.) of retroplacental clot. Ergometrine, 0.5 mg., and morphine, ¼ gr. (16 mg.), were given intramuscularly. The delivery was completed at 4.25 a.m.

A quarter of an hour after delivery about a pint (570 ml.) of watery non-clotting blood was expressed on rubbing up the uterus. The patient became shocked and immediate blood transfusion was begun. The first pint of blood was given rapidly and a second bottle started. In spite of further administration of ergometrine a continued trickle of non-clotting blood continued from the vagina, and expression a few minutes later produced a further half-pint (285 ml.) of non-clotting blood. At 5 a.m. she was becoming more deeply shocked and a third pint of blood was

started. The uterus was then packed firmly with 6-in. (15-cm.) gauze. There was no improvement in her condition and by 6 a.m. watery blood was draining copiously through the pack, and, despite the fact that the uterus was well contracted, it was evident that the pack was not serving any useful purpose. At this stage transfusion with fresh blood was begun, pending the arrival of fibrinogen. The transfusion of fresh blood did not result in any control of the bleeding. At 6.10 a.m. the clotting-time was measured by the Lee and White method; at eight minutes a minute fragment of clot had formed, but the remainder of the blood did not coagulate.

At 6.45 a.m. 2 g. of fibrinogen was given intravenously (human fibrinogen from the Blood Products Unit of the Lister Institute). A quarter of an hour later all bleeding had stopped and the pack was removed from the uterus. (On careful consideration it is estimated that the total blood loss in this case was about 45 oz.—1,420 ml.) At 7.10 a.m. the blood showed complete clotting in four minutes and the clot was stable. An hour later the clotting-time was eight minutes.

At 10 a.m., after no further vaginal bleeding, the urine was free from albumin and the blood pressure was normal. The puerperium was complicated by a severe right-sided femoral thrombosis, which responded well to a paravertebral block. The patient was discharged home well on May 10, the thirty-third day after confinement.

Obstetric Comment (Dr. E. W. L. Thompson).—From a clinical point of view the following features of this case should be particularly stressed: (1) the characteristic nature of the blood coming from the vagina; this was thin and watery with no formed clot, and quite unlike the blood lost in cases of atonic post-partum haemorrhage or from a traumatic source in the lower segment or cervix; (2) the complete failure of ergometrine to control the bleeding, although the uterus seemed to be well contracted after its administration; (3) the failure of a firmly applied intrauterine pack to prevent further bleeding; and (4) hysterectomy, as a last resort, was under consideration as a possible means of controlling the haemorrhage, all the usual methods having failed. In view of the blood findings and the dramatic result following the administration of fibrinogen it is now realized that the operation could have resulted in uncontrollable oozing from the operation site.

Discussion

Severe post-partum haemorrhage is a well recognized complication of accidental haemorrhage. Of a total of 67 fatal cases of severe accidental haemorrhage analysed by Sheehan and Moore (1952), four had moderate and four had severe post-partum haemorrhage. Seven of these eight patients died within 14 hours of the onset of the accidental haemorrhage. All these patients were gravely shocked, but in at least three instances death was due partly to the post-partum haemorrhage. At the time these cases occurred it was thought that the haemorrhage was due to uterine atony, but in the light of modern observations it seems very probable that the real cause was an unrecognized incoagulability of the blood. In the past year at the Rotunda Hospital 64 cases of accidental haemorrhage have been encountered, and on clinical grounds 18 of them were classified as severe. Among these 18 cases two had post-partum haemorrhage of incoagulable blood; this includes the present case, in which blood loss was severe. The conclusion may be reached that severe haemorrhage as a result of incoagulability of the blood is not very common after accidental haemorrhage and probably occurs in only about 5% of severe cases. However, it should be pointed out that degrees of coagulation defects may be present without clinical manifestations.

The important fact that the tendency to post-partum haemorrhage is associated particularly with *severe* accidental haemorrhage has also been emphasized by Weiner *et al.* (1950, 1953), although Stevenson *et al.* (1953) describe cases of haemorrhage following accidental haemorrhage which were of only "moderate" severity.

The incoagulability of the blood follows the accidental haemorrhage and does not precede it (Weiner *et al.*, 1950); certainly in all cases the retroplacental haematoma is clotted. The coagulation defect is essentially transient and usually does not last more than 24 to 36 hours. Before delivery there is thus a danger of continuation of the retroplacental haemorrhage; Weiner *et al.* (1953) suggest that artificial rupture of the membranes has a beneficial effect on the coagulation mechanism at this stage, but Stevenson *et al.* (1953) say that the blood may remain incoagulable until delivery. The more serious complication is that the condition may continue long enough after the delivery to cause severe post-partum haemorrhage or bleeding from a section wound. In the present case, at the time of the post-partum haemorrhage the blood taken from the general circulation was incoagulable *in vitro*.

The actual defect of the coagulation mechanism seems to involve various factors, or probably a combination of them. (*a*) There is a fibrinogenopenia. Weiner *et al.* (1950, 1953) carried out serial fibrinogen estimations and established that there is a quantitative fibrinogen deficit. This may reach dangerous levels as early as one hour after the onset of accidental haemorrhage, or it may progress more slowly over a period of several hours. The critical level of plasma fibrinogen below which blood is incoagulable is stated to be in the region of 100 to 150 mg. per 100 ml. (Stevenson *et al.*, 1953; Weiner *et al.*, 1953). (*b*) The blood prothrombin falls slowly, and may be down to a third of its normal level at about eight or nine hours. (*c*) A fibrinolysin is present for an indefinite period, usually at about four to six hours after the onset of the accidental haemorrhage. This is identified *in vitro* by the dissolution of clot shortly after it has formed.

The reason for this disturbance of the coagulation mechanism is not yet settled. Some workers believe that the reduction of fibrinogen is due to the activity of a fibrinogenolysin or fibrinolysin. Others believe that it is due to a sudden and excessive usage of fibrinogen as a result of clotting in the body. Dieckmann (1936) postulated that the site of this was in the formation of the large mass of retroplacental clot. Schneider (1952) has suggested that multiple tiny thrombi are formed throughout the vessels of many organs as a result of the leakage of thromboplastin from the placenta into the general circulation, and that the body fibrinogen is used up in the formation of these thrombi. Some experimental evidence to support this hypothesis has been given by Seegers and Schneider (1951).

It has been mentioned that fibrinogenopenia may occur without any clinical evidence of bleeding. Nevertheless there is always the possibility that the fibrinogen will continue to diminish and that clinical manifestations will then appear. Tests have therefore been devised to detect "subclinical" fibrinogen depletion. Schneider (1952) employs a simple test to detect fibrinogenopenia; serial dilutions of the whole blood are made and the highest dilution in which there is a visible clot is the fibrin titre. Weiner *et al.* (1953) describe another simple test. Venous blood is collected in a test-tube and kept under observation. If no clot forms or if the blood fails to produce a normal-sized stable clot, this is regarded as enough evidence of a reduction in circulating fibrinogen. In certain cases there is formation of clot, but this dissolves again in a short time. The authors state that this instability of the clot is closely related to the tendency of the patient to haemorrhage. It occurs whenever the plasma value for fibrinogen is reduced to levels of 100 to 150 mg. per 100 ml. or in the presence of a fibrinolysin, or as a combined effect of both these changes. They find that if the clot remains stable for an hour at 37° C. the patient is unlikely to suffer further haemorrhage.

From the literature it appears that for satisfactory treatment of severe fibrinogenopenia it is necessary to administer 2 to 10 g. of fibrinogen intravenously. In the present case no determinations of the fibrinogen content of the blood were made, but within 20 minutes after the administration

of only 2 g. of fibrinogen the previously incoagulable blood formed a stable clot *in vitro* and the clotting-time was normal. Similar cases have been recorded by Weiner *et al.* (1950, 1953). There seems to be no doubt that the intravenous administration of fibrinogen is a very efficient treatment for this condition, and that 2 g. is probably the smallest useful amount. In cases with continuing bleeding, or in cases in which the tests show a subclinical fibrinogenopenia, the administration of fibrinogen can be repeated until the clotting mechanism is normal. It is clearly advisable that a supply of fibrinogen should be available in all obstetric hospitals.

It might reasonably be anticipated that adequate blood transfusion would be a satisfactory method of curing this fibrinogenopenia, since blood transfusion can restore normal coagulation in those non-pregnant cases suffering from congenital absence of fibrinogen (Biggs and Macfarlane, 1953). However, in the particular type of acquired fibrinogenopenia described here, blood transfusion is not a successful line of therapy. It is the practice in this hospital to give at least 3 pints (1,700 ml.) of blood to all patients with moderate or severe accidental haemorrhage as soon as they are admitted, but this treatment failed to control post-partum haemorrhage in the two patients mentioned in this paper. The same failure has been noted by other workers.

Summary

A case of severe post-partum haemorrhage following accidental haemorrhage showed incoagulability of the blood. This defect of the clotting mechanism is a not uncommon complication of accidental haemorrhage. It can and should be identified before delivery, so that specific treatment by the intravenous administration of fibrinogen can be given.

My thanks are due to Dr. E. W. L. Thompson, Master of the Rotunda Hospital, for his help with the case report; to Dr. W. E. R. Hackett, Director of the National Blood Transfusion Service, Dublin, for supplying the fibrinogen; and to Professor H. L. Sheehan, who read the script and made many valuable suggestions.

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A startling report on alcoholism among children was made last month by Dr. SUZANNE SERIN to the Academy of Medicine in Paris. Her suspicions were first aroused by the case of a boy, aged 7 years, who was referred on account of character difficulties and temper tantrums. Close questioning drew from him the admission, "J'ai peur, je vois le soir des ailes, non des mains, des choses blanches qui dansent sur la commode de ma chambre; c'est épouvantable," an answer that led to inquiries about his drinking habits. His parents told Dr. Serin that he drank about a litre of undiluted wine a day, and sometimes, "parce qu'on le trouve nerveux," a glass of port with two yolks of egg beaten into it. Since that case Dr. Serin has always inquired about the alcohol consumption of the children she sees, and in her paper she quotes three similar cases as examples of what she has found. One of the most interesting features of this infantile alcoholism is that it occurs among well-off, cultured families, not, as might be expected, in bad homes where the parents are drunkards.

CRYOGLOBULINAEMIA WITH CEREBRAL PURPURA

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In 1947 Lerner and Watson proposed the term "cryoglobulin" for an abnormal blood protein which undergoes reversible precipitation on exposure of the serum to low temperatures. Barr *et al.* (1950) described the clinical and pathological features of a patient who suffered from recurrent attacks of Raynaud's phenomenon, and whose blood contained on various occasions 4.9 to 9.8 g. of cryoglobulin per 100 ml. In a review of the literature these authors found eight other instances of high-grade cryoglobulinaemia; since then further cases have been reported by Lucey *et al.* (1950), Rörvik (1950), Blades (1951), Luckey *et al.* (1951), Cugudda (1952), Muirhead *et al.* (1952), McFarlane and Dovey (1952), Griffiths and Gilchrist (1953), and Hutchinson and Howell (1953).

This paper records the occurrence of cerebral purpura in a patient with cryoglobulinaemia, an association, to our knowledge, not hitherto described.

Case Report

A man aged 56 was seen in the out-patient department complaining of pain in the lower part of the chest of two months' duration. Clinical examination was negative and blood counts were normal. Four months later he attended again and was admitted to a medical ward for investigation.

The patient was found to have moderate pallor of the skin and mucous membranes. The spine, thorax, and shoulder-girdles were extremely tender on pressure. *X*-ray examination showed collapse of the eleventh and twelfth dorsal vertebrae; in the remainder of the skeleton there were numerous round translucent areas typical of multiple myeloma. The urine contained 1+ albumin but no Bence Jones protein. Sternal puncture showed a cellular marrow, 79% being myeloma cells of varying degrees of maturity. It was difficult to obtain samples of venous blood owing to its greatly increased viscosity. When samples of venous blood were allowed to stand at room temperature (25° C.) clot retraction was slow and imperfect, and the serum settled into two layers of approximately equal volume; the upper was a straw-coloured fluid and the lower a firm pearly-white gel. On heating to 37° C. the gel liquefied, and on subsequent cooling it again became solid. Long needle-shaped crystals formed when a drop of warmed serum was allowed to cool on a slide. The formol-gel test, carried out on the fluid fraction of the serum, was strongly positive. Laboratory investigations showed: haemoglobin, 11.3 g. per 100 ml.; erythrocytes, 3,000,000 per c.mm.; E.S.R. (Westergren), 141 mm. in one hour; E.S.R. (Wintrobe), 14 mm. in one hour; cold agglutinin titre, 1:4; serum calcium, 17.2 mg. per 100 ml.; blood urea, 113 mg. per 100 ml.

The patient's condition rapidly deteriorated, and he sustained several pathological fractures of the ribs during a fit of coughing. Eight days after admission he was given 7 mg. of nitrogen mustard by intravenous injection. On the following day he lapsed into coma. Retinoscopy revealed papilloedema with engorged veins and extensive retinal haemorrhages. Death occurred 16 days after admission.

During the last week of life venepuncture was possible only with a warmed syringe and needle; on standing at room temperature the entire serum became a firm gel. Diluted blood in an erythrocyte pipette showed marked pseudo-agglutination, and blood films could not be made owing to excessive rouleau formation.

The serum protein levels were estimated on three occasions:

	(1)	(2)	(3)
Albumin (g. per 100 ml.)	3.6	4.2	3.4
Globulin ,, ...	5.5	6.0	7.9
Total ,, ...	9.1	10.2	11.3

On the third occasion electrophoresis showed that the high value for serum globulin was due to an increase, mainly in the γ fraction:

α_1-globulin, 0.78 g.	β-globulin, 1.17 g.
α_2-globulin, 1.68 g.	γ-globulin, 4.22 g.

At necropsy the heart and great vessels were intrinsically normal, but contained casts of firm opalescent material. There was extensive oedema of the lungs. The kidneys were pale and swollen, and were separated from their capsules by a fluid exudate. Many pathological fractures were noted in the ribs and vertebrae, and the marrow of these and of the other bones was replaced by reddish-brown gelatinous tumour tissue. The brain was swollen, and section following formalin fixation revealed scattered petechial haemorrhages, mainly affecting the white matter, especially in the internal capsules and cerebral peduncles.

Microscopically the bone marrow was largely replaced by myeloma cells, and infiltrations of these cells were also present in the spleen and renal cortex. The renal tubules showed epithelial damage; many contained casts of crystalline protein material with surrounding giant-cell reaction. A number of vessels in sections from various organs contained "thrombi" formed of a peculiar hyaline acidophilic material; this substance was histologically identical with the larger casts formed in the heart and great vessels, and had evidently precipitated during cooling of the body after death. The small cerebral vessels also contained hyaline material, and each had an associated perivascular haemorrhage. Frozen sections stained with scharlach R showed no evidence of fat embolism in the brain.

Discussion

The association of high-grade cryoglobulinaemia with multiple myeloma and other varieties of plasmocytosis has been increasingly recognized during recent years. Among the more common clinical features of the condition are acropurpura and Raynaud's phenomenon (Wintrobe and Buell, 1933; Flemberg and Lehmann, 1944; Lucey *et al.*, 1950). Cugudda (1952) described a case of multiple myeloma and cryoglobulinaemia in which, following radiotherapy, extensive gangrene of the right leg developed; at necropsy multiple arterial and venous thromboses were found. Hutchinson and Howell (1953) reported a case with extensive gangrene of the digits.

Raynaud's phenomenon and peripheral gangrene occur also in patients with high serum titres of cold agglutinins; this has led several authors to comment on a possible relationship between cryoglobulins and cold agglutinins. However, the common clinical features can be adequately explained on the basis of the mechanical obstruction of vessels in the extremities which occurs at suitably low environmental temperatures, in the one case by masses of agglutinated erythrocytes (Marshall *et al.*, 1953) and in the other by casts of precipitated cryoglobulin.

There is only one report in the literature of extensive precipitation in visceral blood vessels. Muirhead *et al.* (1952) described a case of plasmocytosis with cryoglobulinaemia in which at necropsy the pulmonary vessels contained masses of precipitated protein undergoing early organization. They suggested that conditions in the lungs might occasionally be such as to cause precipitation of the globulin.

In the present case the most remarkable feature was the widespread cerebral purpura, a finding which has not previously been described. Histological examination showed that the haemorrhages were secondary to occlusion of the small vessels by masses of eosinophilic protein precipitate, similar in appearance to that found by Barr *et al.* (1950) in the bone marrow and the lumina of blood vessels and by Muirhead *et al.* in the pulmonary vessels. It seems that these changes in the cerebral vessels were due to the terminal flooding of the circulation with cryoglobulin. We can, however, suggest no explanation for the restriction of the circulatory changes to the brain and retina.

The patient studied by Hutchinson and Howell was on one occasion admitted to hospital with sudden loss of consciousness, from which he made a gradual recovery with no neurological sequelae. These authors were uncertain whether the patient's severe, though reversible, disorder was related to the presence of cryoglobulins in the blood; it may well have been due to lesions similar to those found in our case, but less extensive.

Summary

The clinical and pathological aspects of multiple myeloma in a man aged 56 are described.

Unusual features of the case were the presence of large amounts of circulating cryoglobulin and the terminal occurrence of purpuric cerebral and retinal haemorrhage due to the precipitation of cryoglobulin in small blood vessels.

We are indebted to Dr. J. T. Lewis for permission to publish this case, and to Professor J. H. Biggart and Professor G. M. Bull for their advice.

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Besides giving abundant statistical information about war pensions, the *Report on War Pensions for the Period April 1, 1953, to December 31, 1953*, published this month, records the transfer of Ministerial responsibility made on August 31 last year. Before then everything to do with war pensions was handled by the Ministry of Pensions. On that date the Health Departments took over responsibility for the medical treatment of war pensioners, while the new Ministry of Pensions and National Service was given the task of administering the pensions. Seven former Ministry of Pensions hospitals and two war pensions hospital units, totalling 2,200 beds, were transferred to the Ministry of Health, as well as the interest of the Ministry of Pensions in the administration of the Spinal Injuries Centre at Stoke Mandeville Hospital, Aylesbury. During 1953 nearly 12,500 patients were admitted to these hospitals. In Scotland there was a similar transfer of artificial limb and appliances centres to the Department of Health for Scotland. The steady decline in the number of war pensions which has been taking place since 1947 has continued. At the end of 1953 a total of 931,023 war pensions were being paid, a decrease of more than 28,000 in the year.

OPTIC ATROPHY IN RHODESIA

AN ANALYSIS OF 50 CONSECUTIVE CASES

BY

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In Southern Rhodesia we have encountered many cases of optic atrophy in Africans, and in a high proportion of them no clear cause could be found. As it is a serious disorder affecting young male adults predominantly, we decided to analyse a series of consecutive cases in which the aetiology was not immediately obvious.

Optic neuritis and atrophy has been known to exist for a number of years in Africa and has mostly been attributed to a deficiency of vitamin B. Wright (1928), in West Africa, referred to dimness of vision associated with pellagra, and Fitzgerald-Moore (1937), from West Africa, also gave a full description of this condition, which usually occurred after symptoms of glossitis, stomatitis, and pruritus of the external genitalia had set in. The vision suddenly became misty, and about two months after its onset ophthalmoscopic examination showed definite pallor of the disks, especially on the temporal side. In more advanced cases a complete optic atrophy developed, when the effect on the vision was usually profound. Fitzgerald-Moore found that in early cases of not more than six months' duration favourable results followed the administration of "marmite," but when the disease had lasted more than a year the response was much less.

In 1948 Dawson, Findlay, and Ward reported five cases of optic atrophy in native soldiers of the Gold Coast who lived on usual Army rations, and attributed it to a deficiency of the vitamin-B complex in the diet. Whereas most of the reports favour a nutritional basis, Boase (1952), who described optic atrophy as being common in the native of Uganda, thought that the cause was not a vitamin lack. Indeed, he failed to discover any obvious reason. Gelfand (1947) similarly referred to the many cases of optic atrophy encountered among the Africans in Southern Rhodesia, and regarded a nutritional disorder as an unlikely explanation for this.

Procedure

The cases with optic atrophy were taken consecutively from the native ophthalmic out-patient department at the Salisbury Hospital. They were predominantly male and were drawn from the industrial and farm-labouring class of the Salisbury area. Also included were labourers from all over British Central Africa and the neighbouring Portuguese East Africa. The diet of these people varies, but is based more or less on the following: 1–2 lb. (450–900 g.) of maize meal a day and 1–2 lb. (450–900 g.) of meat a week, with a variable amount of beans, ground nuts, and little or no fresh vegetables.

The types of optic atrophy were classified according to the ophthalmoscopic appearances based on the six descriptive categories of Duke-Elder (1940). (1) *Post-neuritic atrophy* following a papillitis and distinguished by the presence of post-inflammatory tissue on the disk. (2) *Simple or primary atrophy* in which the entire disk is greyish white and clear-cut, the remainder of the fundus being normal. (3) *Vascular atrophy*, distinguished by extreme attenuation of the vessels, as in occlusion of the central retinal artery. (4) *Temporal atrophy*, following retrobulbar neuritis or compression, and distinguished by temporal pallor of the disk. (5) *Consecutive atrophy*, following choroido-retinal disease; this is typically seen in the last stages of pigmentary degeneration of the retina, and is characterized by a yellow waxy colour of the disk and extreme attenuation of the arteries. (6) *Glaucomatous atrophy*, distinguished by the presence of cupping of the disk. Groups 5 and 6 were excluded from the series, as the cause in these cases was not in doubt.

Method of Examination.—Each patient was first examined in the ophthalmic out-patient department, where his visual acuity, fields of vision, and pupillary reactions were recorded together with a description of the eye-grounds. If other ophthalmic disease was present this was also noted. The patient was then admitted to the medical ward, where a full examination was conducted. This included a history and physical examination, with special attention to the nervous and cardiovascular systems. Each case underwent lumbar puncture, the pressure was recorded, and the fluid was investigated for its protein, cell, and chloride content. Blood was taken for the Wassermann test, and a routine sugar and urea estimation was made on each blood sample. An *x*-ray examination of the skull was also carried out (antero-posterior and lateral views). The urine and stool specimens were examined chemically as well as microscopically. As expected in a study of this nature, allowances must be made for the difficulties ordinarily encountered in African practice as regards the accuracy of the clinical history.

Clinical Findings

Of the 50 cases in this series 32 were classified as post-neuritis atrophy, 12 were of simple or primary atrophy, and 6 had temporal and vascular atrophy. Two cases were followed to necropsy.

Case 3.—A waiter aged 48, from a Salisbury hotel, complained of a sudden loss of vision of the left eye some months before reporting to the clinic. He had a pale left disk with shallow cupping, extreme attenuation of the arteries, and an atrophic retina, the right fundus being normal. He died suddenly three months later. At necropsy a large haemorrhage into the left internal capsule was found. The cause of the atrophy was ascribed to endarteritis with occlusion of the left central retinal artery.

Case 25.—This patient complained of sudden loss of vision and severe headaches six weeks before she reported to the clinic. The right fundus showed a white disk with the lamina cribosa obscured, the vessels, macula, and peripheral retina being normal. In the left fundus a white disk with clear-cut margin was found, the lamina cribosa being clearly seen. Radiographs showed enlargement of the pituitary fossa. No visual fields could be determined, as the blindness was absolute. She died one week after admission, the necropsy revealing a glioma of the left frontal lobe.

In two more cases the aetiology of the atrophy seemed to be reasonably definite.

Case 9.—A man aged 25 had very gross cupping of both disks and associated atrophy of the left optic nervehead. Full ophthalmic examination revealed no evidence of glaucoma and the medical examination was negative: his case was classified as primary cavernous optic atrophy (Schnabel, 1892).

Case 11.—A fat young man of 20 had complained of poor vision for some months. Examination revealed a bitemporal hemianopia with macular sparing and temporal pallor of the right disk. There was marked enlargement of the pituitary fossa. Unfortunately, on hearing that the treatment advised was surgical he asked to be discharged, and the exact nature of the lesion was not established. The provisional diagnosis was Fröhlich's syndrome.

Post-neuritic Atrophy.—Of the 32 patients exhibiting post-neuritic atrophy, 20 maintained that the onset of blindness was gradual and 12 said it was sudden (within two weeks being taken as the limit of sudden onset). The ages of the patients varied between 13 and 65, the average being 40. Most of these patients were males, only seven being females. The blood Wassermann reaction was positive in 13 cases

(40%) (Table I), but the reaction of the cerebrospinal fluid was negative in all. Eleven (34%) had changes in the cerebrospinal fluid (7 had an increase of protein, 7 a pleocytosis, the main cell being the lymphocyte or monocyte, and in 4 the pressure was raised). Obvious signs of vitamin-B deficiency were present in only three of the patients, but as they had been blind for at least a year these changes could have occurred because of the difficulty of ensuring proper feeding.

TABLE I.—*Post-neuritic Atrophy Cases. Showing the Number with Blood Wassermann and Cerebrospinal-fluid Changes*

No. of cases	32 (100%)
No. of cases with C.S.F. changes (protein or cell increase)	11 (34%)
No. of cases with +W.R. in blood	13 (40%)
No. of cases with +W.R. in C.S.F.	—

TABLE II.—*Primary Optic Atrophy Cases. Showing the Number With Changes in the Blood Wassermann and Cerebrospinal Fluid*

No. of cases	11 (100%)
No. of cases with C.S.F. changes	2 (18%)
No. of cases with +W.R. in blood	4 (36%)
No. of cases with +W.R. in C.S.F.	0

Primary Optic Atrophy.—Of the 11 cases of primary optic atrophy—excluding Case 25, with the left frontal lobe tumour referred to above—seven claimed the loss of vision to have appeared suddenly and four gradually. Four of the seven with sudden onset gave a history of a severe blow to the eye, after which the vision was completely lost, but radiographs of the skull showed no sign of bony injury in the orbital region, and ophthalmoscopically there was no evidence of damage to the eye apart from the primary optic atrophy. The other eye was normal in all four cases. The ages of the patients varied from 15 to 55 years, the average being 29. The cases were predominantly male, there being only one female case. The blood Wassermann reaction was positive in four (36%), but in the cerebrospinal fluid the reaction was negative in all cases. In two there were changes in the fluid (both with a pleocytosis). Three cases showed skin changes of pellagra, but again the changes could have followed the blindness.

Discussion

Several features stand out from the above facts. Post-neuritic atrophy was by far the most common type of atrophy, the majority of the remainder being simple or primary atrophy. The most striking feature, however, was the high rate of positive blood Wassermann reactions coupled with the corresponding negative findings in the cerebrospinal fluid. The causes of the optic atrophy are considered below under four main headings.

1. General Inflammatory Conditions

Syphilis.—In a population with a high incidence of syphilis, this must be taken very seriously into consideration as an aetiological factor, and the suggestion is that a large number of cases of optic atrophy in Africa to-day are syphilitic in origin, though they show few or no signs of involvement of the nervous system. The incidence of syphilis as determined by the Wassermann reaction in a series of 1,500 consecutive admissions in the same hospital was 19% (Gelfand, 1947). Willcox (1949) estimated the incidence in the general African population in Southern Rhodesia to be about 15%. The percentage of positive blood Wassermann reactions in our post-neuritic atrophy cases was 40%, and in those with primary optic atrophy 36%. These figures seem significant when compared with the general incidence of syphilis. The Wassermann reaction of the cerebrospinal fluid was negative in every case.

Purely from an ophthalmic consideration there were several features which favoured a syphilitic basis. The fields showed concentric contraction rather than central scotomata. Occasional ocular nerve palsies were noticed, and, unlike the usual case of optic neuritis with a good prognosis for vision, secondary atrophy generally developed and bilateral blindness was a common sequel.

A large number of the patients gave a history of having had injections, though few could say whether these were antisyphilitic or not. Some of them mentioned a previous history of venereal disease, though very few had stayed to complete the course of treatment, and, as approximately 36.5 kg. neoarsphenamine was used in one year (1952–3) in the treatment of African patients in Southern Rhodesia, it is reasonable to suggest tentatively that a number of these cases represent a neurorecidive reaction following inadequate treatment for their original venereal complaint.

The association of normal neurological findings with a clear cerebrospinal fluid in the great majority can only be taken to mean that these cases represent a very localized retrobulbar or papillary neuritis in which the brain and meninges escape implication. This parasyphilitic manifestation with no other evidence of nervous involvement has been reported outside Africa (McIntosh *et al.*, 1913; Head and Fearnsides, 1914).

Neurotropic Viruses.—The possibility of a neurotropic virus was borne in mind. Boase (1952), of Uganda, puts forward this as a suggestion only, but we thought it unlikely because of the absence of any sign of infection such as fever and because of the frequently normal cerebrospinal-fluid findings. Disseminated sclerosis is an extremely rare condition in Africa, and no case in this series was thought to be due to it. It is included here for convenience.

2. Endogenous Toxins

Following Acute Infective Diseases.—Malaria, pneumonia, dysentery, and typhoid are all common acute infections in African hospital practice. Optic atrophy, however, has not been reported as an important complication of these diseases. In our series only four cases gave a history of severe illness prior to the onset of the blindness. None of these were admitted to hospital in the acute phase, and no particular infection was traced on admission.

Septic Foci.—In only one patient was this considered to be a possible cause. She complained of a severe bout of toothache involving the first premolar tooth on the upper right side, which caused oedema of her face and right orbit. Only after she had noticed, one month later, the loss of vision of the right eye did she have the tooth removed; the blindness, however, remained.

Metabolic Changes.—Anaemia, diabetes, etc., did not seem to play any part in the aetiology in this series. The blood counts were on the whole within normal limits and no case had an abnormal blood sugar or a raised blood urea.

3. Nutritional Causes

It seems unlikely that poor nutrition has *per se* produced many of the cases of optic atrophy in this series. The majority showed no sign of malnutrition on examination.

The staple diet of the native population is maize meal—of which 1–2 lb. (450–900 g.) a day is eaten, and meat (almost always beef) 1–2 lb. (450–900 g.) a week. This is often supplemented by dried beans, 1 lb. (450 g.) a week, and salt 4 oz. (110 g.) a week. Ground-nuts, sweet potatoes, fresh vegetables, sugar, and bread occasionally are added. Taking 7 lb. (3.2 kg.) of maize meal, 2 lb. (900 g.) of meat, and 1 lb. (450 g.) of dried lima beans a week as an average, this would give an approximate daily intake of 74 g. of protein, 34 g. of fats, and 385 g. of carbohydrates; giving 1,994 calories.

The vitamin-B intake was estimated as adequate. Although not showing any particular deficiency that might be expected to result in an optic atrophy, this intake is probably too low to sustain manual labour.

Defective vision associated with symptoms of pellagra, glossitis, scaly itching of the scrotum, and mental and other nervous manifestations as described in Africans by Wright (1928) from Sierre Leone and from Nigeria by Fitzgerald-Moore (1937) were not seen. Nor did our series bear much relationship to a series of cases of optic atrophy published by Wilkinson and King (1944) from the Far East. In these series of cases the primary foodstuff was rice—in contradistinction to the basic maize meal of our cases.

As a contributory cause, however, it is considered that malnutrition may play a part. In Cases 29, 36, 42, and 48 unilateral optic atrophy followed a severe blow in the region of the eye concerned. In no instance was the blow sufficient to have left any radiological evidence of bony damage, nor was any ocular damage seen apart from the optic atrophy. It seems possible that where a severe concussion injury has caused damage to the optic nerve the nutritional level may be too low to repair the damage and atrophy may result.

One of our cases (No. 46)—that of a soldier aged 37 who complained of the fairly sudden onset of blurring and dimness of vision soon after arrival in Egypt—showed points of similarity to a series of cases from the Middle East (Spillane and Scott, 1945). The majority of these cases retained good physical health, and the skin, heart, lungs, and gastro-intestinal tract were not affected. Within a year of this soldier's return to Rhodesia his vision was reduced to R. 6/36, L. 6/24. His disks showed evidence of post-neuritic atrophy, no central scotoma was demonstrated, his fields being apparently full, but the use of a Bjerrum screen at 2 metres was not made.

There was no significant increase in the number of cases admitted towards the end of the dry season and the beginning of the rains, when food supplies became exhausted. It is at this time of the year that we see, for example, many cases of pellagra, night blindness, and scurvy.

4. Exogenous Toxins

Methyl alcohol, arsenic, and quinine are probably the main toxic agents with which the indigenous population may come into contact. As has already been mentioned, arsenic may play an important part after inadequate treatment of syphilis. Quinine and methyl alcohol blindness were not encountered in this series.

It is possible that a native medicine—not divulged by the patient—may play a larger part than is suspected at the moment. We failed to discover any definite addicts such as the case of optic neuritis in a Qat addict in Somaliland described by Baird (1952).

Summary

Fifty consecutive cases of optic atrophy in Africans from British Central Africa have been analysed. Purely ophthalmic causes, such as chorio-retinal disease with consecutive optic atrophy, and glaucomatous optic atrophy, have been excluded from the series, as the cause in these cases was not in doubt.

Thirty-two of the series were found to be of the post-neuritic atrophy type and 12 were of the primary optic atrophy type. Vascular and temporal atrophy made up the balance of cases.

Various aetiological factors have been considered. In four patients—two of whom died—it was possible to ascribe a definite cause. Of the remainder, it was thought that syphilitic optic atrophy, but with no other neurological lesion, was a probable cause in the majority. A disorder of nutrition does not seem to be an important cause of optic atrophy in Central Africa.

We wish to thank Dr. R. M. Morris for his permission to publish this paper.

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SHIGELLA FLEXNERI ENZOOTIC IN CAPTIVE RHESUS MONKEYS

BY

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The occurrence of dysentery among the rhesus monkeys at the Clifton and West of England Zoological Society's gardens in Bristol proved to be associated with a type of *Shigella* organism which is rarely found in the human population in Great Britain. As the outbreak presents some other interesting features it is reported here.

Macaca mulatta, the rhesus monkey, is kept in the "monkey temple" at the Bristol Zoo. This is an erection in the centre of a concrete pit, well away from direct contact with the public, although the latter can drop food to the monkeys if they wish. The first colony to occupy this temple arrived in 1929. There were 80 monkeys, and many of them died from a disease then regarded as ulcerative colitis, which closely resembled the condition we are now describing as shigellosis. In 1932 the colony began to die from tuberculosis and all had to be destroyed. In the spring of 1933 a second colony arrived, this time without intestinal disease; but again they acquired tuberculosis, and the remaining monkeys had to be destroyed in 1935. In 1936 a third colony of 70 young ones came. They bred well, and showed no signs of intestinal disease or of tuberculosis. However, furious fighting broke out in 1950 and many died of wounds. They were mostly quite old by now, so they were destroyed, except for eight young ones which were kept, and the new colony about which this paper is written was put in with them. In 1949 one monkey of the third colony had died with diarrhoea, and *Sh. flexneri* had been isolated from its faeces, but was not typed. The eight remaining monkeys appeared fit, and it was hoped they did not harbour the organisms.

Cook (1953) reports on rectal swabs taken from 339 freshly imported monkeys received by the Ministry of Supply. From these *Shigella flexneri* type 103 (4a) was cultured once, type 103 Z (4b) 40 times, and type Z twice; *Shigella sonnei* 24 times; *Shigella schmitzi* 50 times, and various other types 6 times. Cook states that bacillary dysentery, pneumonia, and tuberculosis are the main scourges of captive monkeys in this country.

The Epizootic

The present (fourth) colony of 103 monkeys was imported by air from Calcutta on March 19, 1951. They were mostly under 2 years old. Eight days after arrival the new young monkeys began to die. The weather was very cold and snowy. Post-mortem examination was carried out in all cases (Table I). The first eight died of pneumonia; then diarrhoea was noticed, and in the three months up to the end of June a further 18 died. Faeces from 15 of these were examined *post mortem*, and *Sh. flexneri* was isolated from 8, and typed in 6 cases as *Sh. flexneri* 103 (4a). In December, 1951, three more monkeys died, the faeces of two of which were examined, and from these the same organism was isolated.

Early in 1952 sporadic deaths occurred, reaching a peak in April with four deaths, one producing *Salmonella typhi-*

TABLE I.—*Isolation of Shigella Organisms*

	Deaths	Monkeys Examined *post mortem* for Dysentery	*Shigella flexneri* Isolated	*Shigella flexneri* Typed 103 (4a)
March, 1951	7	—	—	—
April–June ,, ...	19	15	8	6
July–Sept. ,, ...	—	—	—	—
Oct.–Dec. ,, ...	4	2	2	2
Jan.–March, 1952	3	3	3	3
April–June ,, ...	6	5	3	3
July–Sept. ,, ...	5	4	3	3
Oct.–Dec. ,, ...	3	1	—	—
Jan.–March, 1953	10	10	5	5
April–June ,, ...	2	1	1	1*
July–Sept. ,, ...	2	2	2	2
Oct.–Dec. ,, ...	2	2	2	2
	63	45	29	26+1*

* Type 103 Z (4b).

murium and two *Sh. flexneri* type 103 (4a). Deaths occurred into the summer, when several monkeys were advanced in pregnancy, and an occasional death was associated in one way or another with this. By winter, dysentery had started again, once more associated with pregnancy, and this time also with *Haemophilus influenzae*, then common in the human environment. *Sh. flexneri* type 103 (4a) was found in four out of a batch of seven dead monkeys, the first four of which were pregnant and the last five of which had worms, so that two were both pregnant and worm-ridden. All except one of this batch had ulcers in the colon, some of the ulcers being very large. The one without colon ulcers nevertheless produced *Sh. flexneri* type 103 (4a). It had a very heavy infection, mainly in the lungs and pleural cavities, with *H. influenzae* (type B), was not pregnant, had no prominent mesenteric lymph nodes, and had only a very small number of *Trichuris trichiura* ova in the faeces. Since that time there have been occasional shigella-positive stools from dead monkeys, and in April, 1953, another type, *Sh. flexneri* type 103 Z (4b), was isolated for the first and only time from this colony. Type 103 (4a) has been isolated four times to date since then (end of December, 1953).

Bacteriology

Faeces and occasional rectal swabs obtained at necropsy were plated direct on to desoxycholate citrate medium and also concentrated in tetrathionate broth. Dysentery organisms were isolated only by direct culture on the desoxycholate plates, but the concentration method was used to safeguard against missing any other intestinal pathogens which might be present. On one occasion *Salm. typhimurium* was isolated by this means.

The isolated dysenteric organisms fermented glucose and mannitol, gave a negative indole reaction, and agglutinated with type 103 (4a) antiserum. The identification was confirmed in most instances by Dr. Carpenter, of the Dysentery Reference Laboratory.

The single isolation of *Sh. flexneri* Boyd type 103 Z (4b) presents an unsolved problem. Antigenically, the relation of type 103 (4a) to type 103 Z (4b) is in the group antigenic components only. Though the subtype 103 Z (4b) does have group-antigen factors in common with type 103 (4a) it also has other factors shared by the types VZ and Z, which type 103 (4a) does not, and there is to date no evidence of change between one Flexner type and its subtype. A possible explanation is that the monkey was infected with type 103 Z (4b) before it entered the zoo, and for one reason or another the type did not spread round the colony. The source of infection of this monkey is unlikely to have been a human contact in this country because of the extreme rarity of this type in human infections in Great Britain.

Reports from Elsewhere

Cruickshank and Bray (1950) reported an outbreak, in the London School of Hygiene and Tropical Medicine, of infection with *Sh. flexneri* type 103 Z (4b) where there was inflammation and ulceration of the bowel, with which several monkeys died. The organism was isolated from one which at necropsy showed no signs of dysentery.

Rewell and Bridges (1948) reported four deaths in 1947 at the London Zoo, and four more at the Institute for Medical Research from the same imported batch, a *Shigella* organism they called "*mulatta*" being isolated. This strain was described as a group variant of type 103, and is certainly type 103 Z (4b). In the zoo animals there was ileal and colonic inflammation, but there were no ulcers. Mesenteric lymph nodes were inflamed. Type 103 (4a) occurs sporadically in the human and is frequently isolated outside Britain. Type 103 Z (4b) occurs in America quite often in man, and has been reported by Carpenter and Sandiford (1952) from a child with dysentery, and from the faeces of a monkey with which the child had contact. Carpenter and Forbes, in a letter from the Dysentery Reference Laboratory in 1953, informed us of the rarity with which types 103 (4a) and 103 Z (4b) are isolated there from human material. However, very many more examples of these types are isolated from primates.

Lesions at Necropsy

The lesions vary greatly, from slight hyperaemia with no lymph-node involvement to very large ulcers with gross lymph-node enlargement. The colon is nearly always the only part affected, and it is the caecal and ascending part which suffers most; the transverse part is affected less often and the descending colon and its most distal reaches very seldom. Sometimes there are deep abscesses beneath the ulcers. There may have been some other cause for these, but none has been found. Worm infestation may play a part. Even with severe infections producing widespread mucosal ulcers there is often no free fluid in the peritoneal cavity, and the outside of the bowel may look quite normal. However, there are always prominent lymph nodes to guide to the affected sites. Chronic infections cause much thickening of the bowel wall, and this fact and the large ulcers suggest that the shigellosis has been present for a long time. The thickening is due to muscle hypertrophy, oedema, and fibrosis. In all cases in which ulceration was present and *Sh. flexneri* was isolated it seemed highly probable that death was due to the shigellosis.

Parasites

Association with worms is not invariable. It happened in the bad-weather epizootic of 1951, and in the period associated with *H. influenzae* in 1953. The animals may nearly all have had worms when they came from India. Certainly, in the lungs of all the first ones which died there was evidence of this in the form of little dry abscesses, which could be seen when the pneumonia epizootic had passed over and the dysentery had begun. The first worms were identified as *Oesophagostomum bifurcum*. By 1953 all these had evidently disappeared, and the whipworm, *Tr. trichiura*, had taken its place. Whipworm ova are still seen in the stools of the monkeys which die sporadically. In the most affected cases worms were found as high as the duodenum, but they usually lived in the colon, attaching themselves by their narrow heads to the sound mucosa between ulcers, and occasionally to the floors of the ulcers where these were not too necrotic. Recently a fresh problem has arisen in the finding of *Giardia lamblia* in the stools of nearly all the dead monkeys, whereas they had not been seen before, although all faeces examined were searched for parasites of all kinds.

Discussion

There are two possible sources whence the organisms might have reached this batch of monkeys in captivity—namely, the handlers and cage-monkeys at Calcutta, or the residue of the previous batch in Bristol—so that there is no evidence here which might help to solve the problem of whether *Sh. flexneri* is confined to captive monkeys or occurs in the wild state. During the three years covered

by this paper no human case of dysentery has produced either *Sh. flexneri* type 103 (4a) or 103 Z (4b) in the Bristol area (in 1952 6,500 specimens of faeces were examined here for dysentery and *Salmonella* organisms). The incubation period is short and no dysentery was observed until eight days after the arrival of the colony in the zoo. Another point of interest lay in the association of death from dysentery with other difficulties encountered by the monkeys—such as extreme youth, worms, bad weather, pregnancy, and *H. influenzae* infection. An uncomplicated dysentery epizootic did not occur. Perhaps both the carrier state and the deaths were encouraged by the associated poor condition. A third point of interest was the persistence of a major infector, *Sh. flexneri* type 103 (4a), in spite of isolated occurrence of *Sh. flexneri* type 103 Z (4b) and *Salm. typhi-murium*. Attempts to eradicate the infection by oral sulphaguanidine proved unsuccessful, confirming Cook's (1953) observations; but injection of streptomycin as recommended by him has not been tried. The monkeys now seem to have reached a state of comparative equilibrium with their dysentery and their parasites.

TABLE II.—*Summary of Data*

No. of monkeys from old colony	8
„ „ young monkeys flown from India	103
Total No. of deaths	63
Faeces examined at necropsy	45
Sh. flexneri isolated from these	29
„ „ typed —103 (4a)	26
„ „ „ —103Z (4b)	1
„ „ not typed	2
Ulceration in colons	33
Diarrhoea	28
Worms	17

Summary

An epizootic appeared to attack a new colony of 103 young monkeys which arrived in Bristol Zoo in bad weather in March, 1951. Sporadic deaths continued to occur into 1953. *Sh. flexneri* type 103 (4a) was isolated from 26 of the 63 monkeys which died. A single monkey gave *Sh. flexneri* type 103 Z (4b) and another gave *Salm. typhi-murium* at necropsy.

The relation of this finding is shown to other afflictions, including *H. influenzae*, pregnancy, and parasites; but emphasis is laid on the association of colonic ulceration with the finding of *Shigella* organisms, and the probability that most of the deaths were due to shigellosis.

Reference is made to other published accounts of similar rhesus monkey infections.

This report was made possible by the co-operation of Mr. R. E. Greed, superintendent of the Clifton and West of England Zoological Society; and of Dr. R. E. Clarke, medical adviser to the Society, who supplied the information about the first three colonies of monkeys. It was carried out under the direction of Professors T. F. Hewer and K. E. Cooper, of the University of Bristol, who made many helpful criticisms. Our thanks are due to Dr. Carpenter, of the Dysentery Reference Laboratory, for her many detailed comments and her continued interest in our work on the monkeys; and to Dr. H. D. Crofton, of the University of Bristol Zoology Department, and Mr. E. Guise, chief technician in the public health laboratory in Bristol, for identifying the parasites.

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Dr. E. H. WALKER, who is retiring shortly from his post as lecturer in public health at Manchester, was recently guest of honour at a gathering of former D.P.H. students. Dr. F. N. MARSHALL presided, and with Dr. T. P. SEWELL paid tribute to Dr. Walker's qualities as a friend and colleague. Dr. Walker was appointed lecturer in 1931.

Medical Memoranda

Infective Hepatitis in a Boys' Hostel

The hostel for maladjusted boys which serves the town and county of Northampton has 20 places for boys whose ages range from 7 to 14 years. On October 13, 1953, a boy fell ill with headache and fever, and jaundice developed three days later. This boy had been admitted to the hostel 20 days previously from a remand home in London, and, although his medical certificate stated that he was not subject to quarantine for any infectious disease, there had, in fact, been three cases of jaundice in the home shortly before he was transferred. As soon as it was ascertained that he was suffering from infective hepatitis he was removed to hospital, the hostel was closed for admissions, and routine precautionary measures were instituted, particular emphasis being placed on the sterilization of crockery and advice on hygiene to the staff and boys. Despite these measures, a second boy, who slept in the same dormitory as the first, was unwell on November 11 and developed jaundice two days later. Finally, on December 14 a third boy, who slept in a different dormitory, developed the disease; in his case jaundice was not manifest until six days after the onset of illness. These two boys also were removed to the infectious diseases hospital as soon as the nature of their illness had been diagnosed.

The general position with regard to the hostel was then reviewed. Since the beginning of the outbreak several of the boys had been discharged to their own homes, and it was appreciated that the maintenance of a hostel with vacant places over a considerable period was to be avoided if possible. Fortunately, through the co-operation of the Public Health Service Laboratory, supplies of gamma globulin were made available, and, after obtaining the consent of the parents, the unaffected boys and staff were inoculated with 9 ml. each of the solution during the first week in January. This was an average dose of 0.11 ml. per lb. (0.24 ml. per kg.) of body weight among the boys and 0.06 ml. per lb. (0.14 ml. per kg.) of body weight among the staff. On January 30 specimens of blood were taken from all the boys and, through the co-operation of the Northampton Hospital Laboratory, were examined for thymol turbidity and bilirubin. The results indicated that none of the boys had suffered from a subclinical infection, and, as no cases of jaundice had occurred after December 14, it was decided to re-admit boys to the hostel.

Control of Spread.—When the incubation period of an infectious disease is as long as five weeks there is a tendency for its infectivity and the control of its spread to be overlooked. The outbreak described in this report illustrates the consequences of admitting to a hostel a child who was incubating the disease. Apart from the illness of the boys, this admission resulted in wasted accommodation and unnecessary expenditure. Moreover, experience has shown that elimination of this infection in a closed community can be very difficult. There would seem, then, to be every reason for imposing quarantine restrictions on contacts of infective hepatitis who are about to enter residential accommodation.

PASSIVE IMMUNIZATION

The value of passive immunization by the administration of gamma globulin in outbreaks of viral hepatitis has been described in several American investigations. Stokes and Neefe (1945) found it to be effective in a dose of 0.15 ml. per lb. (0.33 ml. per kg.) of body weight; Havens and Paul (1945), by administering the gamma globulin earlier after exposure, found that a dosage of only 0.08 ml. per lb. (0.18 ml. per kg.) of body weight was required; while in an outbreak in a Chicago orphanage Stokes (1953) ascertained that doses as small as 0.06 ml. per lb. (0.14 ml. per

kg.) of body weight gave adequate resistance. Apart from its influence on the dosage, however, the time factor is of importance, since it appears that immunization, to be effective, should be given earlier than six days before the onset of symptoms.

Although gamma globulin has been used to control outbreaks of infective hepatitis in America, this appears to be the first occasion on which it has been used in this country. Indeed, as yet there has been no evidence to indicate that gamma globulin obtained from blood donors here contains sufficient antibodies to be of any immunizing value. The outbreak described, while in no way proving the efficacy of gamma globulin, does, however, suggest that it is a potent agent in controlling the spread of infective hepatitis. This is of considerable economic value in closed communities where infective hepatitis entails the restriction of admissions; and it may be that increased supplies will enable the use of gamma globulin as a protective agent to be more fully exploited in the future.

I should like to thank Dr. C. M. Smith, county medical officer, for his advice and help in preparing this report.

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Deputy County Medical Officer of Health, Northamptonshire.

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Scurvy

Frank scurvy is now almost a clinical curiosity in this country. The following case report is therefore of interest and worthy of publication.

CASE REPORT

A postman, aged 56, was admitted to the Royal Surrey County Hospital on July 22, 1952. He had lived in southern England all his life, except for one short period of service with the Army in France during the 1914–18 war, and up to the onset of his present illness had always enjoyed good health.

The present illness started in 1945, when he began to experience epigastric pain occurring approximately one hour after meals. A barium-meal *x*-ray examination confirmed the presence of a gastric ulcer and he was given medical treatment in a local cottage hospital. With treatment he became completely symptom-free, and after discharge he decided to restrict himself to a diet consisting mainly of steamed fish, eggs, bread-and-butter, and milk puddings. He avoided all fruit and vegetables except for an occasional small quantity of mashed potatoes. At no time was his diet supplemented with vitamins. He remained very fit on this diet until two weeks before admission, when he began to complain of lethargy and aching in the muscles of the legs. After approximately 48 hours the legs became swollen and bruises appeared; these slowly spread so as to involve both legs diffusely. At no time has he complained of epistaxis or soreness of the gums, but on close questioning he did admit to some dyspnoea on exertion.

The patient stated that he thought his illness had been precipitated by the recent death of his wife, which, he said, had caused him considerable worry and extra work.

On examination he was pale and of average stature. There was a low-grade pyrexia of 99.6° F. (37.6° C.), with a pulse rate of 90. He was edentulous, but the mouth, throat, and tongue appeared quite normal. In the chest, abdomen, and central nervous system there were no definite abnormal physical signs, and in the cardiovascular system the only abnormality discovered was a markedly positive Hess capillary fragility test. The skin on the upper parts of the arms and thighs showed evidence of early follicular hyperkeratosis, and the legs were grossly discoloured by a haemorrhagic rash in which three types of lesion could be identified. These can best be described as small circumfollicular purpuric spots, and larger raised, red, tender plaques approximately 2 to 3 cm. in diameter; there were also large subcutaneous extravasations of blood involving the major part of the feet, legs, and thighs.

Apart from the individual lesions mentioned above, the legs were not tender at the time of examination, although the patient did state that the calves had been tender prior to admission.

On investigation the following results were obtained: haemoglobin, 41% (6.56 g.); R.B.C., 2,200,000; colour index, 0.93; M.C.D., 7.1 μ; W.B.C., 4,200 (73% polymorphonuclears, 25% lymphocytes, 2% monocytes). The platelet count was 280,000 per c.mm. and the prothrombin index 83%. The bleeding-time was 2½ minutes, and the clotting-time 9½ minutes (venous blood). The blood Wassermann reaction and Kahn test were negative. The urine contained a trace of albumin and small numbers of red cells and leucocytes, but no casts were seen and culture was sterile. The stool was cultured for pathogens with a negative result. An *x*-ray film of the tibiae revealed no bony or periosteal abnormality.

An ascorbic acid saturation test was performed, the technique of which was to give 10 mg. of ascorbic acid per kg. body weight at 9 a.m., followed by a determination of the total urinary excretion of ascorbic acid between 1 and 3.15 p.m. It is stated that a fully saturated person should excrete 50 mg. or more during this 2¼-hour period.

Synchronous with this test a daily reticulocyte count was done in order to determine the haematological response to ascorbic acid only, no iron being given. The results are shown in the Table.

Day	Ascorbic Acid Excreted in 2¼-hour Period	Reticulocyte Count
1	1·3 mg.	1·8%
2	1·92 ,,	2·2%
3	2·32 ,,	3·4%
4	4·27 ,,	6·6%
5	3·97 ,,	4·2%
6	8·26 ,,	7·0%
7	8·77 ,,	8·4%
8	31·3 ,,	8·6%
9	64·0 ,,	8·6%
10	50·0 ,,	11·7%

After the completion of the saturation test, treatment was continued with ascorbic acid. By the time of his discharge, after three weeks in hospital, the patient was feeling extremely fit, the lesions on the legs had completely resolved, and his haemoglobin had risen to 80% (12.8 g.). He has since been seen again as an out-patient, and has remained quite well.

COMMENT

The diagnosis in the above case can be in no doubt, as the clinical findings, the ascorbic acid saturation test, and the response to treatment were all confirmatory.

Although subclinical deficiency of vitamin C is not uncommon in this country, scurvy is rare. If one considers the possibility that a number of people may be living on inadequate self-imposed diets, such as our patient was doing, this is perhaps surprising. One can only suppose, however, that very few people, except obsessionists, would in fact avoid all fruit and vegetables so completely as to cause frank scurvy. Nevertheless, the possibility of scurvy occurring in a patient on a diet is a very real one, and consideration should therefore always be given to the vitamin content in any prescribed diet.

I wish to thank Dr. H. Bell, under whose care the patient was admitted, for permission to publish this case.

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Reviews

NATURAL PHILOSOPHER

Thomas Young, Natural Philosopher, 1773–1829. By the late Alexander Wood, M.A., D.Sc. Completed by Frank Oldham, M.A., B.Sc., F.Inst.P. With a memoir of Alexander Wood by Charles E. Raven. (Pp. 355; illustrated. 30s.) Cambridge: University Press. 1954.

The bare outlines of the career of Thomas Young make incredible reading. Born in 1773 of a Quaker family, he had a studious upbringing and was in contact with learned men from the earliest days. At the age of 14 he was an accomplished Latin and Greek scholar and could discuss the merits of classical authors with mature scholars. He very quickly added French, Italian, Hebrew, Arabic, and Egyptian to the list, and later became proficient in German. He studied medicine in London, Edinburgh, and Göttingen. Returning to this country from the last city, he decided it was essential to obtain an English qualification, and he therefore entered Emmanuel College in 1797. He rapidly graduated and came to London. For a time he worked as a scientist, first of all as professor of physics at the Royal Institution, where he delivered a series of lectures. In these he foreshadowed a number of his own discoveries and also the discoveries of others made later in the century. Elected a Fellow of the Royal Society at the age of 21, he became Foreign Secretary in 1794 and held this post until his death.

He was appointed to a number of Government Commissions and in 1818 became secretary of the Board of Longitude and presided over the committee that produced the *Naval Almanack*. He was physician to St. George's Hospital and had an extensive private practice, although it must be admitted that he was not so successful in this sphere as he was in others. His research work left an indelible mark on science, as evinced by the household expression "Young's modulus." He laid the foundation for the theory of colour vision and played a fundamental part in establishing the wave nature of light. He also wrote on life assurance and on a number of clinical topics. In addition to all this he opened the way for the interpretation of the Egyptian hieroglyphic inscriptions. His work on the famous Rosetta Stone provided the first sure passage to the understanding of the history of ancient Egypt, and we can say that we owe our knowledge of Egyptology to-day to his researches.

These then are the bare facts, and one wonders how it would be possible in a book of normal size to give an adequate picture of this fascinating career. It is astonishing that very little of a collective nature had been written about Thomas Young. Two years after his death Hudson Gurney published a short memorial and 20 years later Dean George Peacock, of Ely, the Lownden Dean Professor of Astronomy at Cambridge, published an edited collection of Young's scientific papers and also wrote the life. The *Dictionary of National Biography* contains an excellent summary, but until the publication of the present volume no modern account has appeared. The present volume was begun 40 years ago by the late Dr. Alex Wood, who devoted the greater part of his life to a study of Young. Unfortunately the author died when ten chapters had been completed. Mr. Frank Oldham, who had himself published a short biography in 1933, was able to add the last two chapters and see the book through the press. Canon Raven writes an appreciation of Dr. Wood.

The book is excellent in every way, being well documented and very full. It describes in detail Young's early life, his studies in this country and abroad, and the development of his various theories. The general reader will naturally turn to the dramatic and romantic story of the Rosetta Stone. This occurs in Chapter 9, and is undoubtedly the fullest account of a general nature available to the ordinary reader. It will be remembered that in August, 1799, some of Napoleon's troops were excavating near a town in the Nile Delta, when a French officer found a stone covered with obviously three different types of writing. Early in 1801 the stone, known as the Rosetta Stone after the village in which it was discovered, came into British possession when the French troops surrendered. It was first housed in the Society of Antiquaries and later removed to the British Museum. Prior to this the French had issued copies to all the principal scholars of Europe. It occurred to scholars that the three scripts might be translations of each other. One was in Greek, one in Egyptian running script, and the third in the characteristic hieroglyphics. Young heard of the stone and eventually obtained access to it. It is not possible in this review to describe the methods which enabled him to effect a translation, but he was able to show that the three scripts all described the same event and from that was able to produce the first reasonable translation of the hieroglyphic language. This is described in fascinating detail, together with the bitter rivalry that occurred between Young and the French scholar Champollion.

To medical readers Chapter 4 will perhaps be the most interesting. This describes Young as physician and medical author. We can see that his heart was not really in medical practice and he appeared to resent the success of others. This astonished him, since he regarded many of the successful consultants of the time as being infinitely inferior mentally. The author shows quite clearly that Young did not possess the necessary humanity and sympathetic appreciation so essential in a good doctor.

This is a work which should certainly be found in every medical library and can be read by medical man, scientist, and general reader with equal pleasure and profit.

E. C. DODDS.

PLAGUE

Plague. By R. Pollitzer, M.D. World Health Organization: Monograph Series No. 22. (Pp. 698; 79 illustrations, including 40 original drawings, 2 folding maps, and 2 coloured plates. Cloth bound, £3 5s.; $10; 40 Swiss francs. Paper bound, £3; $9; 36 Swiss francs.) Geneva: World Health Organization. 1954. Sales agent for U.K.: Her Majesty's Stationery Office.

This monograph presents in book form a series of 10 studies which appeared at intervals from November, 1951, to September, 1953, in the *Bulletin* of the World Health Organization, together with two annexes and an index. Each of the studies deals with a separate aspect of the subject, so that the history and present distribution of plague, its bacteriology, immunology, pathology, laboratory diagnosis, hosts, vectors, clinical aspects, epidemiology, and control and prevention all receive a due measure of attention. The author, whose own work on plague while he was in China entitles him to approach the subject with authority, has made a comprehensive and critical compilation from all the more significant articles which have appeared on each of these subjects. Each section carries its own references, and the extent of the author's researches may be gauged by the fact that these total just under 1,900. The first annex is a list of reservoirs and vectors, and occupies some 21 pages, while the second, written by F. G. A. M. Smit, of the British Museum (Natural History), deals with the identification of fleas.

This is a monumental work which cannot be summarized in short compass. It will prove of great use to those engaged in the study of any of the many aspects of the plague problem, and will be a standard book of reference for many years to come. It must not be forgotten, however, that the earlier studies were completed some years ago. Unfortunately one of these is on immunology, and in this subject considerable work has been done and progress made in the last few years, particularly in relation to the immunizing properties of capsular antigen. It is interesting to follow the advances which have been made in rodent control and even more so in vector control, where the new insecticides have proved to be of the greatest value. In the realm of therapy, while antiserum still has its place, sulphonamides and antibiotics, particularly streptomycin, have been used with good results.

The author is to be congratulated on producing a book which will find a place on the shelves of every medical library and will lighten the labours of those who set out to study this subject.

J. S. K. BOYD.

INFANT FEEDING

Infant Feeding and Feeding Difficulties. By Philip Rainsford Evans, M.D., M.Sc., F.R.C.P., and Ronald MacKeith, M.A., D.M., F.R.C.P., D.C.H. Second edition. (Pp. 277; 66 illustrations, including 2 coloured plates. 12s. 6d.) London: J. and A. Churchill Ltd. 1954.

This is probably the best 12s. 6d. worth of paediatric literature available to-day. The fact that a second edition has followed so closely on the first is proof of its value, and this edition is even better than the first. In the space of less than 250 pages the authors have contrived to cover the whole ground of infant feeding, both natural and artificial, and, in addition, to include a number of pathological conditions affecting infants' gastro-intestinal tracts. There is a comprehensive series of appendices. The chief changes in this second edition are the replacement of the references to Grulee's 1934 Chicago report on the health and survival of breast-fed infants by that of Douglas in this country in 1950, additional references on the subject of cracked nipples, and a doubling of the penicillin dosage recommended for breast abscess. The cunning insertion of the word "wheat" before "starch" brings the treatment of coeliac disease right up to date. The chapter on artificial feeding has been partly rewritten, and dried preparations are now given precedence over liquid milk. The recommendations are so sound and explicit throughout that it comes as something of a surprise to find the authors advising, in Appendix 8, that iron mixtures should be added to the feeds; it is probably wiser always to give medicines apart from the feeds.

The book is well produced, and to all who undertake the care of infants will provide a fund of information of value to paediatricians, practitioners, students, and nurses.

WILFRID GAISFORD.

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE

The School and the Site. By Catherine M. Clark, M.A., and James M. Mackintosh, M.D. London School of Hygiene and Tropical Medicine, Memoir No. 9. Foreword by Andrew Topping. (Pp. 105+xii; 44 illustrations. 21s.) London: H. K. Lewis and Co. Ltd. 1954.

Bloomsbury in the course of centuries has undergone many changes. In the reign of Henry III one William Blemund was lord of this manor. Blemund's land became changed into Blemundsbury and finally into Bloomsbury. In 1545 Thomas Wriothesley, the Lord Chancellor, who became Earl of Southampton in 1547, owned the land. Later, the two great houses of Bedford and Montagu had the property, and gave their names to the various streets and squares that were built thereon. In the seventeenth and eighteenth centuries Bloomsbury was an aristocratic quarter, but in the fields behind Montagu House, now the British Museum, there were sinister happenings. As Thackeray relates in *Esmond* and *The Virginians*, it was a noted place for duels; and in the Long Fields there was "the Brothers' Steps" or "the Field of the Forty Footsteps," where two brothers killed each other over a worthless woman.

When fashion went westward, Gower Street and Keppel Street became the homes of professional people, chiefly lawyers. Constable, the artist, lived in Keppel Street, and Anthony Trollope, the novelist, was born there in 1815. Later, the street declined to lodging and boarding houses. Then, as the twentieth century was born, came a period of desolation. The leases fell in and the houses were demolished. The site was bought for a projected "Shakespeare Memorial Theatre," but the sums subscribed were insufficient to build it. The first world war came and the site was granted rent-free for a Y.M.C.A. hut by the Shakespeare Committee. Eventually, Thespis had to give way to Hygeia. This historical account of the Bloomsbury area is ably told by Miss Clark and adorned by a wealth of illustrations. Then Professor Mackintosh takes up the pen. He tells how Lord Athlone's Committee reported to the Minister of Health in 1921 and recommended "that an Institute of State Medicine should be established by the University of London in which postgraduate instruction should be given in public health, forensic medicine, industrial medicine, and in medical ethics and economics." Forensic medicine was dropped, and, in spite of the efforts of Lord Trenchard, the late Sir Bernard Spilsbury, and others, London, unfortunately, still lacks an institute of forensic medicine.

The main proposals went ahead under the chairmanship of Sir Alfred Mond, and the London School of Hygiene and Tropical Medicine, a school of the University of London, was made possible through the munificent gift of over two million dollars from the Rockefeller Foundation. When the School was formally opened by the Prince of Wales on July 18, 1926, the British and American flags flew side by side "at the dawn of a new era of preventive medicine."

Many expert minds went to the school's development and organization. Under the direction, first of Sir Andrew Balfour, then of Sir Wilson Jameson, Professor J. M. Mackintosh, and Professor Andrew Topping, the school has extended its activities and influence in the 25 years of its life. Its divisions and departments—the Ross Institute of Tropical Medicine with Sir Malcolm Watson as Director, the Bureau of Hygiene and Tropical Diseases, the library, the museum, the field station, hospital facilities, research activities, and the period of restoration, 1947–52, after the bombing in May, 1941—are all described. The teaching and work of the pioneers of the school in its first generation are omitted, doubtless as subjects for a later memoir. The authors are to be congratulated on a worthy memorial.

ARTHUR S. MACNALTY.

PHYSIOLOGY OF MAN

The Physiology of Man. By L. L. Langley, M.A., Ph.D., and E. Cheraskin, M.D., D.M.D. (Pp. 609; 180 figures. $5.50 or 44s.) New York, Toronto, London: McGraw-Hill Book Company, Inc. 1954.

"The book is dedicated to the proposition that learning can be fun." It is at two levels, and so its real contents are apt to be misunderstood. The illustrations are a feature of the book, and are excellently drawn by Mr. Paul Patterson to the author's instructions. Nevertheless, many of them are unnecessary, though sprightly, and not lacking in humour, which, however, is incidental, and of the type nowadays popular with illiterates. That is the one level.

The other level, the text matter, is of an entirely different nature, and, once the distraction of the illustrations is overcome, turns out to be sound, well written, and up to date in outlook. The dogmatic statements which appear here and there are understandable enough, and indeed necessary in a book of this standard and size, as they make for clarity and definiteness of presentation.

It is difficult to know for what type of student the book is intended. The type for which the illustrations mean much—for example, the figure illustrating the fact that water will flow faster from a tap if the mains pressure is raised—will possibly expect that the photographs of sufferers from elephantiasis or pellagra are intended to be funny too, and such readers, or lookers, might find the text tedious by contrast. The less frivolous student, on the other hand, might well think that the evident ability of the illustrator could better have been employed in really illustrating the excellent text matter more fully.

Probably all this turns on a difference between the American and the British sense of humour. I have myself been known to crack a joke (on alternate years) in lectures, but have rarely attempted to mummify it in print, and lack the ability to do so pictorially.

C. LOVATT EVANS.

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MEDICAL RESEARCH FOR THE TROPICS

The Colonial Development and Welfare Act of 1945 made financial provision for the promotion of research on divers subjects in British possessions overseas. To carry out one section of these plans a Colonial Medical Research Committee, composed of members nominated in part by the Medical Research Council and in part by the Colonial Office, was set up under the chairmanship of the secretary of the Medical Research Council. Its terms of reference were to advise the Colonial Office and the Medical Research Council on medical research in the Colonies; in practice it became responsible for initiating or sponsoring medical research projects. At the time of its inception many schemes inspired by the requirements of war were nearing their end, while the withdrawal of the British medical services from India, which actually took place in 1947, loomed on the horizon. Inevitably the focus of interest moved to Africa, where, because of the menace of disease to man and domestic animals, great tracts of land lay underpopulated and underdeveloped. Diseases such as malaria, trypanosomiasis, helminthic infestation (filariasis, onchocerciasis, and schistosomiasis), dysentery of all kinds, virus infections (among them yellow fever), leprosy, relapsing fever, and other less familiar conditions were prevalent, and much was still to be learned about their control and cure. Opportunities for fruitful research were to be found on every hand.

How have matters progressed in the intervening years? Some of the answers to this question are to be found in the recently published "Report of the Medical Research Council for the Year 1952–3," which reviews developments in the organization of medical research for the Tropics. There are two requisites for successful research: well-equipped laboratories and an ample establishment of able investigators. Good progress has been made in setting up laboratories. At Fajara, in the Gambia, the Medical Research Council (with financial assistance from colonial development and welfare funds) has established a large field research station; this was at first concerned solely with problems of nutrition, but has now become an independent unit in which research on any of the numerous tropical diseases which occur in that area can be carried out by the Council's staff or by guest workers. At Kumba, in the Cameroons, a helminthiasis research unit has been set up, primarily to work on loaiasis but with a free hand to investigate other worm diseases. At Mwanza, in Tanganyika, extensive laboratories have been built to house a filariasis research unit and an East African medical survey unit which is making a general assessment of the health conditions of native races. Here also ample accommodation is available for guest workers. The two lavishly equipped Rockefeller virus research laboratories, one at Entebbe, in Uganda, and the other at Yaba, in Nigeria, have been handed over to the Colonial Office and come under the jurisdiction of the Colonial Medical Research Committee. A hot-climate physiology research unit at Oshodi, in Nigeria, a research laboratory concerned with nutritional and related problems in Makerere College, in Uganda, and other minor interests complete a list of establishments which, taken in conjunction with research units working under local governments, provide reasonable facilities, though admittedly of different standards of excellence, in most of the territories. Elaborate institutes have also been created for research into trypanosomiasis in man and animals, but this subject comes under the aegis of a special committee.

Unfortunately the second requisite, the recruitment of an adequate staff of trained research workers, has not been fulfilled. In the recently published annual report (1953) of the East African Medical Survey the director remarks: "It is a depressing fact that we have been given the finest of tools but cannot do the job because of lack of manpower." Part of the original plan of the Colonial Medical Research Committee was to create a Colonial Medical Research Service into which suitable candidates could be recruited. This was framed on the same lines as the Colonial Medical Service, and came into force in 1949. The salaries offered were based on those of the scientific staff of the Medical Research Council, plus the usual allowances, leave, and other privileges granted to workers in the Tropics. However, it soon became clear that something was amiss, for in the ensuing years the number of entrants was disappointingly low. The reasons for this are complex, and relate partly to doubts about the future security of a career in a service which comes mainly under the control of the local governments, and partly to fears that facilities for research might be disappointing and that a worker stationed permanently overseas might find difficulty in keeping abreast of contemporary developments through isolation from other workers and lack of access to the best scientific libraries.

Steps have now been taken to overcome some of these objections. In the present unsettled political conditions which prevail in Africa it is not easy to budget for the future, but an attempt has been made to secure stability by placing the administration of research initiated by the Colonial Medical Research Committee under interterritorial bodies which, although carrying strong representation from the local governments, are administratively independent of them, being responsible to the Secretary of State. Such a body, the West African Council for Medical Research, has already been established by ordinance, and steps are being taken to follow suit in East Africa. These councils will function as autonomous financial and administrative authorities responsible for all the research schemes initiated by the Colonial Medical Research Committee in their areas. They will obtain funds from contributions made by the home Government under the Colonial Development and Welfare Act, by the local governments, and perhaps from private bequests.

On the scientific side explicit recognition has now been given to the need for fundamental research in the United Kingdom on problems of tropical disease. All applied research, and much basic research requiring easy access to the actual material which is being studied, must obviously be carried out on the spot, and will continue in accordance with existing arrangements. But much important research can be successfully conducted only with the help of special facilities which it would be neither economical nor perhaps even feasible to supply to tropical laboratories. To provide for this, the Secretary of State has arranged that financial support can be given to home-based research. The money available will be allocated on the advice of the Colonial Medical Research Committee, either as grants to university departments or other research organizations for work which may be done both at home and, if necessary, overseas, or to maintain research workers specially recruited to work either at home or overseas as occasion demands. For administrative purposes these latter workers will be made members of the staff of the Medical Research Council. Thus there will be opportunities both for the field research worker, whose investigations call for permanent residence in the Tropics, and for his more academic colleague, whose fundamental work can best be done with the facilities and inspirations of a well-equipped department at home, but who, if necessary, can go overseas to complete his investigations, perhaps in one of the laboratories equipped to accommodate guest workers. For the training of the embryo research worker the committee have at their disposal a certain number of studentships which can be awarded for a period of two years, during which the student, who must of course previously have acquired satisfactory qualifications, will be trained in a recognized department dealing with the subject in which he is interested. If he proves his worth he will subsequently be recruited into the Colonial Medical Research Service.

Research in the African territories is in no way confined to the projects initiated by the Colonial Medical Research Committee, and much good work, more particularly in the nature of applied research, is being done under the auspices of the local governments. Though in many ways it would be preferable to have all medical research schemes under unified control, this is at present impracticable.

It would be foolish to hope that this new approach to research in tropical diseases will bring an immediate spate of recruits: but it does appear that a career in this subject can now be recommended with some degree of confidence. The scope which it offers is unique, and the door is wide open.

MEDICAL RESPONSIBILITY

The doctrine that a medical man is solely responsible for the patient in his charge seems to our profession not only self-evident but fundamental to good medicine. It matters not whether the doctor is employed by a hospital, a local authority, or an industrial concern; he recognizes that when patients are under his care his duty lies to those patients, not to his employer, and that the relationship between doctor and patient is a personal one that admits of no third party intruding except in consultation. So far, in spite of all that recent judgments in the English courts have done to impair this relationship, it has escaped serious injury. This was perhaps partly because of the hope that English law might yet turn from the course it had taken and once more allow the doctor, as heretofore in Scotland, to stand on his own feet and to accept responsibility for his actions. Unfortunately the reverse has happened, and Scottish law has now taken the first fatal steps of surrender to the lead given by the English courts. By a decision of the First Division of the Court of Sessions, reported in the *Journal* this week at p. 308, boards of management of Health Service hospitals are made vicariously responsible for the negligence of resident members of medical staffs in the performance of their professional duties.[1] The judgment is concerned with resident medical officers, but future decisions in the Scottish courts may well make Health Service hospitals there, as in England, vicariously responsible for other categories of hospital doctors.

The court had two cases before it of alleged negligence by resident medical officers, and the hospital boards of management had been sued for damages as well as the doctors. The hospital authorities had previously been absolved in the lower courts from vicarious responsibility. Delivering the present judg-

ment (with which his two colleagues on the bench concurred), the Lord President, Lord Cooper, posed these crucial questions: "Are medical personnel in a class apart from all other skilled persons? Is a distinction to be drawn between skilled persons who belong to a 'profession' and those who do not?" Lord Cooper did not give a direct answer to them, but the argument that he developed will not evoke much sympathy among medical men. The essence of the matter, he said, was that those doctors were (our italics) "*whole-time salaried officials, prohibited from private practice*, normally resident on the hospital premises and subject as such residents to a measure of disciplinary control." They were subject now, he continued, as in the past, "in the exercise of their professional judgment and skill only to the supervision and the direction of the medical hierarchy under whom they were assigned duties." Lord Cooper then turned to the relationship between the hospitals and the patients created by the Health Service Act, and concluded that the older Scottish decisions were outmoded. One of these[2] (which he referred to) is worth recording here for its succinct expression of what doctors believe that relationship ought to be: "All the managers undertake is to provide an efficient, heated, clean, wholesome sick-house, equipped with the necessary furniture and fittings for the reception of patients; to employ a competent staff; and to provide the necessary medicine and food. But they do not, as I understand any conceivable view of their functions, undertake to treat or to dose, or to operate upon any of those who come into their institution." It is indeed difficult to reconcile this outmoded conception with the one, now found to be more appropriate to the times, of a hierarchy of salaried officials to whom duties are assigned.

In some respects the implications of this judgment seem to be more far-reaching than those of the similar English judgments, for its conclusions are explicitly founded in part on the situation created by the National Health Service, whereas in England the courts had turned in this direction before the Health Service began. It was in 1942 that an English hospital authority was found liable for the negligence of a radiographer[3] and in 1947 for the negligence of a student house-surgeon.[4] Even so, judges in the English courts have on occasion since 1948 made observations which suggest that, had it been necessary, they would have been willing to rely on the National Health Service Acts to lead them to the same conclusions. Lord Cooper dwelt in his judgment on a new obligation created by the Act and regulations, "an obligation on the State . . . to treat the patient and not merely to make arrangements for his treatment. . . ." To medical men the meaning of these words must be difficult to interpret. How can the State treat patients? If this is what the Health Service Acts enjoin, then their alteration by Parliament is an urgent necessity, for the quality of medicine will suffer by every diminution of the doctor's responsibility. The short answer to Lord Cooper's questions is that doctors are indeed distinct from all or nearly all other skilled persons in that they are individually responsible for the health and life of the patients in their care, and neither the State nor any other employer can take over that responsibility without damaging the patient's interests.

[1] *Scotsman*, July 22, 1954.
[2] Lord President Clyde, in *Reidford* v. *Magistrates of Aberdeen*, 1933.
[3] *Gold* v. *Essex County Council*.
[4] *Collins* v. *Hertfordshire County Council*.

THE END OF SPENS?

The Minister of Health, Mr. Iain Macleod, has at last (July 22) openly in Parliament declared the Government's attitude to the Spens Report on the remuneration of consultants and specialists and of hospital medical staff, and has confirmed, if any confirmation were needed, the views of those who saw in the recent agreement between the Staff and Management Sides of Whitley Committee "B" something which cut right across the Spens recommendations and so across the policy of the British Medical Association, reaffirmed with overwhelming majorities by the Representative Body at Glasgow but three weeks ago. Mr. Macleod was asked by Mrs. Mann "what assurances were given to hospital staffs, including senior hospital medical officers, registrars, etc., as to the acceptance of the Spens recommendations; how far he proposes to accept these recommendations; and what steps are being taken to implement the Spens' report as applicable to hospital staffs."[1] Mr. Macleod's written reply was as follows: "The recommendations in the Spens' report formed the basis for the terms and conditions of hospital medical staff which were agreed with the profession and published in 1949. In answer to the second and third parts of the Question, I should like to make clear the Government's views that the remuneration of medical practitioners cannot be settled by reference only to the recommendations of a report made six years ago before any experience had been gained of the National Health Service. As my right hon. friend the Chancellor of the Exchequer said in this House on July 2, 1952, remuneration must be determined after taking into account all relevant circumstances. In the light of this, increased rates of pay have recently been introduced for hospital medical staff under an agreement with their representatives."

This written reply, together with Sir John Hawton's letter to the Secretary of the B.M.A. and Mr. Macleod's minuted reply to a question from Sir Russell Brain,[2] can leave little doubt that

[1] *Hansard, House of Commons*, Thursday, July 22, Vol. 530, No. 154.
[2] See leading article, *British Medical Journal*, May 15, 1954, p. 1139.

the present Government has repudiated the Spens "Report of the Interdepartmental Committee on the Remuneration of Consultants and Specialists" published in May, 1948, and presented then to Parliament by the Minister of Health and the Secretary of State for Scotland. The Spens Committee completed its task after holding sixteen meetings, and its conclusions were based on statistical information obtained by the Evidence Committee under the guidance of Professor A. Bradford Hill. The Report, evidently, was not something dashed off in a hurry to meet a printer's deadline. The "relevant circumstances" Mr. Macleod now refers to were described in the Spens Report as "the necessary adjustments to present-day values of money" and "the increases which have in fact taken place since 1939 in incomes both in the medical and in other professions." What other "relevant circumstances" there may be Mr. Macleod does not state, so one is left to infer that they are political. What is at stake here is a matter of principle, not sums of money. The present Government has broken faith with the medical profession by repudiating the Spens Report, the implementation of which has just been urged once more by the Representative Body of the British Medical Association. If there were to be any modification of the basis of remuneration in the two Spens Reports, accepted by both medical profession and Government only six years ago, then this must be openly arrived at and agreed not only by the Government but by the profession as a whole. Once the medical profession, in this or in any other matter, gives way on principle to the all-powerful State, it can expect but short shrift in the future.

ILLNESS IN INFANCY

In a public lecture delivered not long before his death, Sir James Spence stated that as time passed he had found his interest increasingly drawn to the problems of aetiology of disease. He was particularly fascinated by "the undiagnosed, at present largely undiagnosable, infections of childhood," and believed that advance of knowledge required an extension of the traditional methods of clinical investigation into the field of epidemiology. But the epidemiology which he advocated was of a special kind: he conceived it, not as the work of a specialist, but as a development of the clinician's interest in the natural history of disease, by close and continuous observation of patients and their families. This conception lies behind the Newcastle survey of one thousand families, initiated by Spence and conducted jointly by the university department of child health and the city public health department. The main object of the inquiry was to keep under review the health and sickness experience of approximately 1,000 children born in Newcastle during two months of 1947. Most of the field work was done by health visitors provided by the public health department, and the medical staff were drawn from the university. The inquiry was intended to continue for at least seven years, and the report[1] now published by the Nuffield Foundation and the Nuffield Provincial Hospitals Trust covers the period from birth to the end of the first year.

A substantial part of the report is devoted to an examination of the morbidity and mortality experience of the children, of whom only one-fifth were free of illness during the first year of their lives. One of the purposes of the investigation was to give a clearer perspective to medical education, and it is noted that there were about 1,400 infections of a kind rarely seen in teaching hospitals, and only 18 illnesses of a type characteristic of traditional clinical teaching (intussusception, meningitis, osteitis). Indeed, the predominant impression left upon the reader is the immense and continuing significance of infectious disease: 86% of all illnesses were infective in origin, and "the incidence of severe infections—especially bronchitis, pneumonia, and gastroenteritis—increased as the standard of living and social status decreased." This observation is consistent with other recent findings,[2 3] and refutes an earlier report[4] that morbidity, unlike mortality, is no longer related to social and economic circumstances. It suggests that a substantial proportion of the illnesses of infancy are preventable. The same conclusion emerges from detailed examination of the 44 deaths, of which 15 were considered to have been avoidable. The report suggests that in Newcastle an infant mortality rate of 23 per 1,000 live births is compatible with present knowledge, if not with present services.

Does the prevention of the avoidable illnesses and deaths depend mainly upon improvements of a social and economic character, or can it be assisted by modifications of the medical services? The authors of the Newcastle report suggest that "the time is now ripe to alter and reform the various institutions which maintain the health of children and prevent or cure their diseases." The improvements during the past half-century they attribute primarily to a raised standard of living, and to wider knowledge of the care of children provided by the various public authorities, and by relatives of mothers. The failure of doctors to play a more conspicuous part in this work is considered to be due to defects of medical education, which must be remedied before a satisfactory service can be set up. Changes proposed in medical education are directed to widening the student's experience of the problems which present in general practice, and include the suggestion that instruction in infectious fevers should be recognized as a direct responsibility of the department of child health. To make this effective new children's hospitals should include wards for infectious disease.

Spence and his colleagues firmly reject the suggestion, made by Parsons[5] and others, that some general practitioners might devote themselves exclusively to the care of children. They do not weigh fully the considerations which have led to this proposal, although in objecting to it they make the valid point that infection in childhood is frequently a manifestation of family infection,

[1] *A Thousand Families in Newcastle upon Tyne*, 1954, London.
[2] Douglas, J. W. B., *Populat. Stud.*, 1951, **5**, 35.
[3] Lowe, C. R., and McKeown, T., *Brit. J. prev. soc. Med.*, 1954, **8**, 24.
[4] Grundy, F., *Med. Offr.*, 1949, **81**, 144.
[5] Parsons, L. G., *Child Health*, 1947, London, p. 14.

and should be considered against a background of knowledge of the whole family. On the controversial matter of the respective responsibilities of local authority doctors and general practitioners for the health of children the authors of the report make no definite proposals. But they are clearly of the opinion that it would be unwise to begin dismantling the existing public health services until we are quite certain that we have something equally satisfactory to put in their place. Instead they propose a change in emphasis within the local authority services, and their hopes for an improved child health service are largely vested in the joint efforts of a better educated generation of family doctors, and health visitors who have added to their present responsibilities the functions of a children's nurse.

IMMUNIZATION AGAINST POLIOMYELITIS

Fundamental to the problem of preventing paralytic poliomyelitis is an understanding of the route by which the virus reaches the central nervous system. If the modern concept is correct—that blood-stream spread is an essential phase after primary virus multiplication in the gastro-intestinal mucosa[1]—and there is increasing evidence to support it,[2] then on purely theoretical grounds an antibody barrier in the blood is more likely to be effective than if the virus invades by purely neural pathways. As resistance is closely related to the presence of antibody, the practical problem is to decide how to produce and maintain antibody at an effective level. Much experience has been gained in recent years in the control of viral and rickettsial diseases by immunization.[3] The value of passive immunization in measles with gamma globulin lies not in complete suppression of the infection, which can be only a temporary effect, but in attenuation of the disease as a consequence of limited virus multiplication. The conditions in poliomyelitis are different, and the use of gamma globulin as a general protective measure is neither feasible nor advisable. Further, since there is not much of it, its use should be limited to carefully selected cases.

Active immunization aims at producing prolonged immunity, and, irrespective of whether inactivated or live vaccines are used, certain criteria must be observed before a vaccine passes from the experimental stage to use in field trials. The first criterion, one of safety, is the foremost consideration, particularly in poliomyelitis. Measured in terms of infectiousness, it means absolute certainty that no live virus remains in a killed vaccine or that a vaccine containing attenuated virus has no capacity to produce paralysis, and also that the vaccine is free from pathogenic properties due to the presence of foreign protein. In addition the vaccine must be a good immunizing agent, containing the appropriate virus strains (all three types in the case of poliomyelitis). Methods of quantitative estimation and biological assay are essential. Finally, it should be possible to produce the vaccine economically. Recent progress in laboratory methods has made much of this possible in the case of poliomyelitis.

Last year Salk and his associates[4] reported their preliminary observations on active immunization of human beings. The vaccine prepared in tissue culture and containing all three types of virus was treated with formalin and contained a mineral-oil adjuvant. As a result of technical improvements[5 6] a more potent vaccine has been produced without the necessity for an adjuvant, since this cannot at present be considered completely safe.[7] The levels of antibody produced with a formalized vaccine are quantitatively much lower if no antibody is present before vaccination than in the immune or partially immune subject, in whom a marked booster effect often occurs.[8] This vaccine is now under trial in the United States, and the results, particularly those pertaining to the length of immunity, will be awaited with universal interest.

Unquestionably the greatest achievements in preventive medicine have resulted from the use of living attenuated vaccines which, as a result of virus multiplication, give long-lasting immunity. In the opening pages of this *Journal* Dr. Herald R. Cox emphasizes the importance of this approach to the problem of preventing poliomyelitis. Two major difficulties present themselves. First, can all three strains of poliomyelitis virus be so modified in the laboratory as to lose their virulence—that is to say, the capacity to produce paralysis—yet maintain their immunogenic properties and remain stable? Secondly, will live virus, after administration, for instance by mouth (which seems the most logical way to give it) change in character on subsequent passage through human beings? Koprowski and his colleagues[9 10] have taken the first step in this approach to active immunization by giving live avirulent Type 2 (Lansing) virus to a small group of subjects by mouth. Sabin,[11] another exponent of living modified virus for immunization, has shown in a preliminary communication that avirulent or non-paralytogenic strains can be produced in the laboratory and that these do not appear to give rise to transmissible virulent virus. Cox considers that mammalian tissue is potentially dangerous because of latent pathogenic organisms and consequently favours the developing chick embryo as a culture medium. One strain (MEF1, Lansing type 2) has already been adapted in this way, and preliminary observations suggest that although virulence of the strain is markedly reduced the immunizing power is retained. These observations of Sabin and of Cox are of the greatest significance, but much work still lies ahead before immunization against poliomyelitis becomes a practical possibility.

THE FACE OF A THOUSAND WRINKLES

The reaction to growing old has varied through the ages. In the time of our grandparents it was a graceful art and adorned the pattern of life. Few pictures were so pleasing as that of the gracious old ladies of the last and the early part of this century, so well portrayed by the late Lord Simon writing of his mother. To-day, in spite of

[1] Bodian, D., *Amer. J. Hyg.*, 1952, **55**, 414.
[2] Horstmann, D. M., McCollum, R. W., and Mascola, A. D., *J. exp. Med.*, 1954, **99**, 355.
[3] Cox, H. R., *Lancet*, 1953, **2**, 1.
[4] *J. Amer. med. Ass.*, 1953, **151**, 1081.
[5] *Amer. J. publ. Hlth*, 1953, **43**, 1384.
[6] Ibid., 1954, **44**, 563.
[7] Freund, J., *et al.*, *J. exp. Med.*, 1953, **97**, 711.
[8] Salk, J. E., *Pediatrics*, 1953 **12**, 471.
[9] *Amer. J. Hyg.*, 1952, **55** 108.
[10] *Proc. Soc. exp. Biol. (N.Y.)*, 1953, **82**, 277.
[11] *Amer. J. Dis. Child.*, 1953, **86**, 301.

increasing longevity, it is too often held to be something of a disgrace, and "the face of a thousand wrinkles" beloved by W. H. Hudson is not beloved by the modern woman. Though the fashion of face-lifting by the plastic surgeon, which once held the headlines, has had a short career, the approach through the endocrines has had a more subtle vogue. Rejuvenation by sex hormones administered internally gave place later to the incorporation of endocrines in cosmetics and has been something of a commercial ramp. The offer to clear wrinkles and imperfections and to keep the face young and the complexion beautiful is an attractive one to the woman approaching middle age.

There is no doubt that the administration of oestrogens locally as well as internally can effect changes in the skin, including influence on hair growth and on keratinization. In addition the local application of oestrogens, apart from causing local changes in the skin and mucosa, may produce general effects from absorption. But it has always been doubtful whether the hormonal creams advertised by cosmetic firms had any effect on wrinkling of the skin in middle age, and now Behrman,[1] as the result of a clinical study on twenty-seven women, concludes that the presence of hormone in the creams had no discernible objective or subjective effect. A noticeable improvement in the appearance of the skin in women with dry skins resulted equally from the use of the base without hormones and from other emollient creams. Even this must offer some consolation to the fair sex and may prevent them from following the example of the men of Grantchester, who, "When they get to feeling old, They up and shoot themselves I'm told."

Wrinkling, thinning, and loss of elasticity and other changes in the texture and appearance of the skin associated with advancing years are mostly confined to exposed parts. Biomolecular studies[2] have shown that the changes are connected with a degradation of connective tissue fibrils, which become short, bent, and frayed, and break down into amorphous material, which is greatly increased. There is an increase of elastic-staining tissue, but this is merely altered collagen, there being only few elastic fibres in the dermis. Such changes are not observed in senile skin except in the exposed areas and are clearly due mainly to the effects of exposure to the elements, especially light. It is not to be expected that these changes would be influenced by the application to the surface of creams containing hormones or anything else.

PREVENTION OF BARBITURATE POISONING

Various suggestions have been made of ways in which the effects of barbiturate poisoning might be avoided, and these have recently been discussed in an article by Koppanyi and Fazekas.[3] The inclusion of a small amount of an emetic with the barbiturate has been found unsuccessful. When ipecacuanha was used[4] it was found not to produce prompt emesis in the presence of large amounts of barbiturates, but was absorbed, and after repeated administration to dogs it produced liver damage and hypoplasia of the bone marrow. Zinc salts on the other hand,[5] when taken with large doses of barbiturates, caused prompt emesis, but could not be used repeatedly because of their toxicity. Purgatives and oxidizing agents were also tried and found unsatisfactory. An ingenious suggestion was made that barbiturates should be incorporated in chewing-gum, and, since the individual would receive the barbiturate only so long as he continued to chew, he would not obtain more than a hypnotic dose, for he would stop chewing as soon as he fell asleep.

A different approach was to use an analeptic. Stimulant substances which would act as antidotes were mixed with barbiturates. The first experiments were made with caffeine. When given by mouth to dogs in doses of 150 mg./kg. together with 35 mg./kg. of sodium pentobarbitone, convulsions occurred, but they did not modify the depressant action of the barbiturate. When the caffeine was reduced in amount to 125 mg./kg. while the sodium pentobarbitone remained unchanged, the dogs behaved as if they were receiving the sodium pentobarbitone alone.

Experiments on mice showed that caffeine, strychnine, nikethamide, amphetamine, and dexamphetamine all failed to protect against barbiturate poisoning, but that both picrotoxin and pentylenetetrazol (leptazol) were more promising. It is this latter substance which Koppanyi and Fazekas consider is most useful. They state that it does not irritate the alimentary mucosa, even when given to man in doses of 200 to 400 mg. t.i.d. for several months. When leptazol was combined with sodium pentobarbitone in the proportion of 3 to 2 it did not interfere with its sedative and hypnotic effect. Apparently leptazol in small doses does not act as a stimulant, for they say that normal subjects given 0.5 to 1.0 g. of leptazol by mouth fell asleep while E.E.G. records were being taken. However, when human subjects took 45 mg./kg. of leptazol and 15 mg./kg. of sodium pentobarbitone, there was an appreciable delay in the onset of sleep, and when it occurred they could be easily roused. Thus Koppanyi and Fazekas conclude that, while leptazol does not interfere with the effect of therapeutic doses of this barbiturate, it protects against overdoses. The following combinations were administered to human subjects daily for one year: 300 mg. leptazol and 100 mg. sodium secobarbitone (quinalbarbitone); 150 mg. leptazol and 100 mg. sodium pentobarbitone. No untoward effects developed as judged by the behaviour of the patients as well as by the periodical examination of their blood and urine. There was no evidence of a tendency to addiction.

Dr. H. Kenneth Cowan, county medical officer of health for Essex and chairman of the Public Health Committee of the B.M.A., has been appointed to succeed Sir Andrew Davidson as Chief Medical Officer of the Department of Health for Scotland.

[1] *J. Amer. med. Ass.*, 1954, **155**, 119.
[2] Tunbridge, R. E., *et al.*, *Clin. Sci.*, 1952, **11**, 315.
[3] *Amer. J. med. Sci*, 1953, **226**, 597.
[4] Radomski, J. L., *et al.*, *J. Pharmacol.*, 1952, **104**, 421.
[5] Miskimon, R. M., and Miskimon, R. R., *Va med. Month.*, 1950, **77**, 119.

PROGRESS IN MEDICAL SCIENCE

ANNUAL REPORT OF THE M.R.C.

Every year now the *Annual Report of the Medical Research Council* contains a section on recent scientific discoveries of importance for medicine. A number of subjects where the council's money and encouragement have increased knowledge are reviewed in fairly non-technical language : in the Report for 1952–3, just published, there is an account of the medical planning that lay behind the success of the Everest expedition, and surveys of such medical matters as high blood pressure, the study of twins, virus infections, cortisone, such developing surgical fields as tissue grafting, hypothermia, and peripheral nerve injuries, while biochemistry is treated in sections on fat metabolism, the pest-killers of agriculture, and general cell metabolism. The Report also contains much information on the individuals and research programmes supported by public money, and the council's various research establishments and the committees which guide clinical trials and other M.R.C. activities. The opening chapter of the Report, a discussion on "Medical Research in the Tropics," is reviewed in our leader columns this week (p. 289).

Planning the Everest Climb

A characteristic of the later phases of the second world war, such as the invasion of Normandy in 1944, was the detailed scientific planning behind every operation. The final successful assault on Everest had the same hallmark. Indeed, British military experience, in its widest sense, was probably all-important. In climbs to high altitude three physiological factors are primary : oxygen, food, and clothing protective against the cold. They were factors already much studied by the R.A.F. and the research establishments at Farnborough, and the oxygen equipment used on the climb, the fruit of this experience, was designed at Royal Aircraft Establishment. The Clothing and Equipment Physiological Research Division of R.A.E. helped with the design of sleeping-bags, tents, and jackets, trousers, and gloves, drawing on experience of Arctic travellers and the Army's bitter winters in Korea. The food rations, for the first time on this kind of expedition, were based on Army "compo" rations and mostly came from Army stores. Finally, a kind of full-scale rehearsal for the Everest expedition was held in 1952, when a group climbed Cho Oyu to 22,500 ft. (6,800 metres) in the Himalayas and made many valuable physiological measurements, particularly of the three primary factors.

It was shown that open-circuit oxygen sets, providing oxygen–air mixtures and disposing of exhaled air to the atmosphere, were the most practical in terms of weight and reliability, and that men could sleep at night in their oxygen masks. For the Everest climb no less than 193,000 litres of oxygen were shipped to Nepal. Breathing oxygen enhanced endurance at all heights over 18,000 ft. (5,400 metres), and climbing was faster at higher altitudes because there was no longer any need to rest every few steps. Recovery from fatigue was much quicker, warmth and sleep came easily at night, and comfort and mental activity of the climbers remained at a good level, thanks to oxygen. Hillary took off his oxygen mask at the top in order to take photographs, but after ten minutes realized that he was becoming clumsy and muddled, which is good evidence that the success of his climb owed a debt to physiology.

Previous expeditions had suffered badly from diarrhoea and from respiratory disease, owing partly to lack of immunity to the local brands of infection and partly to lack of adjustment to the local diet, with its frequent curries, tsampa (stone-ground parched barley), dhal (a kind of lentil), and large quantities of sweet tea. It was therefore decided to spend longer in the area before actually attempting the assault, in order to get acclimatized, and the 1953 party had a kind of climbing holiday for three weeks at Thyangboche (13,000 ft.—3,900 metres) before starting on Everest, with very greatly improved health. Pressure cookers were an innovation which made possible the cooking of yak meat and potatoes above 18,000 ft. (5,400 metres), and a much greater proportion of the total food eaten was taken out from England in special packs. It was known that each man needed between 5 and 7 pints (2.8 and 4 litres) of fluid daily, and this time his water consumption, calories, salt intake, and vitamins were carefully watched.

Nylon and rubberized fabric were useful materials for clothing and kit, and kapok insulated the uppers of the climbing boots. Lightness, perfect fit, and temperature insulation were achieved with great care, and no one had frost-bite or cold feet. All the climbers were studied to follow the physiological changes induced by the stress of climbing, and samples of blood and expired air were collected and sent back to England for analysis. The results of this research have yet to appear.

Hypertension ; Twins

In an ageing population two diseases of the cardio-vascular system become increasingly important : arterio-sclerosis, leading to narrowing of arteries and insufficient blood flowing to vital organs such as heart and brain ; and hypertension, increasing vasoconstriction against which the heart fights till it fails. Twenty years ago Goldblatt showed that constricting one renal artery in the dog after removal of the other kidney leads to hypertension, and later work explained this as due to the production of an enzyme, renin, from the remaining damaged kidney, and its action on a plasma globulin to produce hypertensin, the true vaso-constrictor. More recently it has become likely that some as yet undiscovered mechanism must maintain the hypertension, once it is experimentally induced, because renin is no longer present in increased amount after the first weeks of the clamp. Nor is renin the explanation of most cases of human "essential" hypertension—for blood taken by catheter from the renal vein contains no extra renin in such patients. Massive blood transfusions from hypertensives into normals do not provoke fresh vasoconstriction.

Another approach to the blood-pressure problem has been a fresh attempt to define normality by the clinical study of a population. It seems that essential hypertension is not an entity, but a label stuck on all individuals who have a blood pressure above some arbitrary level, in defiance of the fact that individuals normally differ in characteristics such as height, intelligence (and blood pressure), a variability which can be described in terms of a mean value for the population and the degree of natural spread (standard deviation) plus or minus. Only outside these limits should we talk of abnormality. Further, it is normal for blood pressure to rise as one gets older, and close relatives resemble one another in both the magnitude of their pressures and the rate at which these increase, so that inherited constitution plays some part in hypertension as a disease.

The inheritance of disabilities is particularly well studied by comparing identical twins. About one adult in 200 has an identical brother or sister. Identical twins are always of the same sex, have identical blood groups, identical eye colour, hair texture, shape of ears, hands, and teeth, and similar (but not identical) finger-prints. In a large unselected series of notifications of poliomyelitis there were 14 pairs of identical twins and 33 pairs of dissimilar or fraternal twins. But five pairs of identical twins had the paralytic form and only two pairs of the fraternal twins were so affected, a difference so big that susceptibility to paralytic poliomyelitis must depend partly on inherited characteristics. In adult pulmonary tuberculosis studied in New York State in 1943, every adult under 30 had nearly one and a half chances out of a hundred of catching the illness. But those with a brother or sister, or fraternal twin, already suffering from the disease had 25 chances in every 100 (1 in 4) of also going down with it. But if one member of a pair of identical twins contracted tuberculosis, the other almost always did too (87 chances in a 100, nearly 9 out of 10). This is a measure of the extent to which susceptibility is inherited. In this series tuberculosis became more than three times more likely where identical twins, with identical

inheritances, were involved, but of course environments also still played a big part. Similar studies have proved quite conclusively that heredity is important in epilepsy, and in mental illness. Seventy-six per cent. of the identical twins of schizophrenics get schizophrenia, but only 14% of fraternal twins of schizophrenics also do so. On the other hand, the fact that 24% of the identical twins of schizophrenics escape the illness is testimony to the fact that environment is also very important.

Grafting Tissues

A skin graft from one human being to another takes only if donor and recipient are identical twins—that is, genetically alike. This means that, though it is easy enough to maintain a skin bank—for skin will keep for over a year in deep refrigeration—it is usually impossible to get the graft to take, because of an immunity response by the host, which is similar to the reaction to incompatible blood. Apparently lymph nodes produce antibodies which do not destroy the graft, but prevent its cells from multiplying, and, though a dose of cortisone will weaken this adverse response, it is of no present practical value. It is part of every individual's inheritance to resist the introduction into his body of cells genetically different from his own.

However, to this rule Professor Medawar and his group have recently discovered an exception, which may eventually lead the way to successful homografting. If the foreign cells are introduced into the host when he is still a foetus, he accepts them and ever after remains tolerant to that particular foreign brand of cell, though still antagonistic to any other variety of foreigner. Thus a brown mouse of strain CBA accepted skin grafts from any white mouse of strain A when he had been inoculated while still a foetus with living A-line cells. This shows that immunity responses can be modified, and therefore that there is hope of one day being able to graft living tissues and even organs from one person to another, and perhaps even from animals to man.

Biochemical Progress

Recent biochemical work, at the National Institute for Medical Research and elsewhere, has revealed some of the functions of vitamins, and emphasized how very greatly the chemistry of the living body is based on a few very simple substances. Thus nicotinic acid, a B vitamin, is made by tissues of the rat, but only if the rat is fed enough pyridoxine and riboflavine (other B-group vitamins). The amino-acid serine is converted into glycine (amino-acetic acid) by an enzyme from the rat, if folic acid is also added to the mixture. Apart from food, glycine is synthesized in the body, but apparently only from serine. It is an important substance, because in turn it is the raw material for making the haem of haemoglobin (and probably other porphyrins, too—as in porphyrinuria), and for making the creatine of muscle, and also for making the important sulphur-containing amino-acid methionine. This last reaction apparently needs the presence of vitamin B_{12}.

Serine, which is hydroxy-amino-propionic acid, and a fairly close chemical relation of the glycine to which it can give rise, also has proved to be the raw material for the body's manufacture of choline (and acetylcholine, therefore) and the phospholipids of brain. Acetic acid, on the other hand, is the building brick for fat and for cholesterol. The mammary gland, for instance, manufactures the fatty acids of milk by tacking one acetic acid molecule to another, adding a third, then a fourth, fifth, and so on to the gradually enlarged compound molecule until the large fatty molecules of butter fat are made. This process can now be performed with isolated enzymes in the laboratory flask.

All this new work has come very largely from the use of radioactive isotopes to study metabolic processes. It is beginning to create a new picture of the way that living cells function, something much simpler and more orderly than could have ever been expected when the enormous chemical complexities of the fats, proteins, starches, porphyrins, steroids, etc., were first realized. These substances are complex, but it begins to seem that they are made from very simple starting ingredients—often from one and the same initial material—and created by ringing the changes on a few stock or standard chemical reactions, which are repeated (as acetic acid is converted into fat) or alternated (e.g., transfer of methyl group, CH_3, obtained from glycine, to make homocysteine into methionine, and ethanolamine into choline). But if such a range of body chemicals can be created with a few simple reactions, then the order in which the reactions occur must be important, and this order must derive from structure. So the physiologist is being increasingly drawn back to the anatomy of the cell, a microscopic, almost a molecular, anatomy, for the further understanding of living functions.

THE PROBLEM OF AN AGEING POPULATION

INTERNATIONAL CONGRESS IN LONDON

The third Congress of the International Association of Gerontology (but the first to be held in the United Kingdom) was opened at Church House, Westminster, on July 19. It was attended by over 350 delegates from 42 countries. After an inaugural session the Congress on the succeeding four days met in sections, in which the subjects for discussion were the biological, physiological, psychiatric, and sociological aspects of old age, and reports were presented from laboratories and research centres in various parts of the world, but especially in the United States.

Opening by Minister of Health

The Congress was formally convened by Professor E. V. COWDRY, of St. Louis, president of the second Congress, who inducted his successor, Dr. J. H. SHELDON, of Wolverhampton.

The MINISTER OF HEALTH (the Right Hon. Iain Macleod, M.P.), who attended to give his blessing to the Congress, described the care of the ageing as "unquestionably the major social problem of our day." It was a problem, he said, as old as time, and yet one that had become much more urgent in recent years, largely because of the success of physicians and surgeons, scientists and chemists, in prolonging life. But to continue existing was not enough; those who were old must be made to enjoy living. "Not survival but happiness is the true fulfilment of your work." The problem was so vast that the State itself could not solve it. In the United Kingdom they were fortunate in having a vigorous voluntary movement which supported and enriched the work of the State. In dispelling loneliness, which was the principal tragedy of old age, voluntary effort could play an important part, and he instanced in particular the friendly work of Women's Institutes.

A vote of thanks to the Minister was accorded on the motion of Professor R. E. TUNBRIDGE, chairman of the Executive Committee. In the evening the Minister gave a reception to the delegates at Lancaster House.

President's Address

In response to a general welcome extended to the visitors from abroad, brief speeches were made, on behalf of their respective contingents, by delegates from Capetown, Calcutta, Washington, Adelaide, and Basle.

Dr. SHELDON, in his address from the chair, spoke of the impending challenge to our social stability as a result of the steady increase in the number of old persons in the community. He stressed two points of special importance. One was the change in the internal structure of the old-age population characterized by an increase in the proportion living beyond the age of 75. The second danger concerned what might be termed the average duration of final incapacity—that is, the ultimate period of life during which an individual might require total "carriage" by the younger members of

the community. The first requirement for meeting this situation was to maintain the general vigour of the old so that they had capacity both to contribute to the common effort and above all to maintain their domestic independence for as long as possible.

Experience of old people both before and after the inception of the National Health Service led him to say without hesitation that the provision of suitable spectacles was far and away the most important single thing that could be done to maintain the useful activity of old people. Alleviation by hearing-aids of the decline in hearing that so often accompanied old age probably came next to spectacles in importance. The argument for the provision of these aids to perception became all the stronger when it was remembered that cerebral mechanisms in old age required a greater sensory input than in youth, and that this was the very period when the special peripheral receptors themselves became so liable to structural defects. A further means of sustaining the vigour of the old lay in attention to their feet. This presented a major challenge to preventive medicine. Finally, the key to physical vigour in many old people lay in their mental state. Nothing sapped physical strength more surely than the mental torpor that followed a loss of interest in life.

Retirement at 65

Dr. Sheldon went on to say that the compulsory retirement of so many men at 65 had led many to feel that this figure possessed an almost mystical sanctity—that it marked a nodal point in the rhythm of life which of itself justified a cessation from previous activities. This was not the case. It was still true in general that a man was "as old as he feels." The average man of 65 still had some years of activity in front of him unembarrassed by the infirmities of old age. Men who derived emotional satisfaction from their occupation and were without alternative outlets would find that continuance in their customary rhythm of life actually helped to hold the ageing process at bay, while a sudden severance had been known to hasten it.

He believed it to be the case that 90% of the old people in Great Britain were still looked after at home. Their domestic care was provided by the old people themselves and by their families and friends. Those who were socially isolated formed the hard core of the nursing and domestic problem of old age. There was an ominous concord of agreement among those with first-hand experience of an apparent decline in family sentiment—an increasing tendency for children to regard the care of an aged relative whose management at home had become tedious or difficult as the proper concern of the State.

"Nevertheless, as a practising physician I am still prepared to declare a deep faith in the existing sense of family loyalty. The sentiment certainly lies deep in human feeling, though it has not the compulsion that attaches to, say, the maternal instinct. . . . We must see that help is given to the family in the places where it is most needed. . . . Nothing makes a family more willing to continue the care of an aged and difficult relative than the knowledge that the community will recognize the need for holidays and for assistance during phases of a final illness which are causing overpowering domestic stress."

The only hopeful and realistic way of facing the future was for the community on the one hand and family and friends on the other to join in an active partnership in the care of their old people. Neither could manage it alone.

Scientific Programme

The Congress then broke up into four Sections dealing with "Biology and Pathology" (*Chairman*, Sir FRANCIS FRASER; *Secretary*, Dr. O. OLBRICH), "Geriatric Medicine and Psychiatry" (*Chairman*, Dr. MARJORY W. WARREN; *Secretary*, Dr. T. S. WILSON), "Sociology and Psychology" (*Chairman*, Miss E. I. BLACK; *Secretary*, Miss M. BUCK), and "Research Committee" (*Chairman*, Professor A. P. THOMSON; *Secretary*, Dr. V. KORENCHEVSKY). The conclusions of these Sectional meetings were presented to a final meeting of the Congress in plenary session on July 23, with the President, Dr. J. H. SHELDON, in the chair.

"Biology and Pathology" was the province of Section I. The highlights of the Sections programme were four symposia, but in addition many individual papers were read and discussed. The first of the symposia was on "Nutrition—Experimental Aspects in Relation to Ageing." On the next day the subject was "Endocrinological Aspects of Ageing with Special Reference to the Female Generative Organs," and finally there were symposia on "Experimental Study of Skill in the Elderly" and "Changes in Total Metabolism and in the Oxygen Supply of Individual Organs as Affected by Age." When it came to presenting the Section's conclusion to the Congress, Dr. OLBRICH had a difficult task, as the discussions had ranged over such a wide and varied field that they defied summarization.

Dr. MARJORY W. WARREN had the same difficulty with Section II, "Geriatric Medicine and Psychiatry." This Section had discussed such subjects as the cardiovascular problems of the aged, neurology in the aged, the effect of ageing on mental and physical capacity, and the treatment and prognosis of psychiatric illness in old age, as well as a large variety of papers on other medical and surgical subjects. Amongst the 74 papers read to the Section, she picked out for particular mention those dealing with conditions which are special problems in old age—vertigo, urinary incontinence, and cardiovascular disorders. There had also been useful contributions on the general rehabilitation of elderly people, from both the medical and the practical point of view.

Social Factors

A more coherent theme distinguished Section III, "Sociology and Psychology," and Miss E. I. BLACK, the chairman, was able to describe the work of the Section more easily. The first session, "Introduction to Social Policy," had set the scene, she said, for the succeeding days' discussions. In the first place, attention had been drawn to the very sharp differences in the age structure in different countries, with the implied existence of rather different gerontological problems; secondly, the importance had been stressed of allowing for psychological and cultural factors in any social approach to gerontology; and, thirdly, some common assumptions about old age had been challenged—for example, the claim that people tend to live much longer than formerly, when in fact the expectation of life at 60 or 65 is not very much greater than it used to be. Some other assumptions that had been challenged were: that everyone wants to go on working after a certain age; that work is necessarily good for everybody's health after a certain age; and that the system of flat-rate contributions and pension benefits in Britain is inevitably the best and most equitable. Time and again in the discussions they had been reminded that neither the old nor the poor could be regarded as an undifferentiated mass: differentiation and individualism were essential in social programmes.

One session, she continued, had been on education for later maturity, and in this they had been shown the potentialities of the new media for mass communication, such as radio and television. There had been a plenary session on the methods and objectives of field surveys. In spite of what had already been done there were simple and important questions still awaiting answers; for instance, we did not yet know the relative costs of providing institutional care or home service for old people, nor did we know what heavy work really meant in relation to old people. In Britain, Rowntree, the successor of Charles Booth, and Dr. Sheldon had succeeded in building a bridge leading from the social survey right into the medical world. "Section III," Miss Black concluded, "has been grateful for the opportunity it has had of showing that this is a bridge which can be crossed in both directions."

Research on Ageing

Professor A. P. THOMSON spoke for the Research Committee (Section IV). There had been three main topics of

general interest. The first was the problem of ageing in the cell itself. In the last few years many new techniques had been discovered for the study of the chemistry of the individual cell, and a number of authorities in this field had discussed the relationship of this work to the question of ageing. Their second topic had led them into the dim borderland between mind and matter. The theme had been "Causes of Mental Inefficiency in the Elderly," and they had tried to discover how closely related were measurable physical data and analysable mental phenomena.

Their last topic had been the problem of the genetical determination of old age: whether length of life was determined by the genes with which their parents endowed them. That was unquestionably true of certain lowly forms of life in a standard environment, but man's environment was seldom standardized. What emerged from the discussion was that the gene is no longer inviolable. "This offers," he said, "a measure of hope to an association such as this—that environment may have effects of greater significance in the expression of the genes than we have hitherto suspected."

Finally Professor Thomson paid a special tribute to Dr. Korenchevsky, the Secretary of the Research Committee, without whose efforts the Section might not have existed at all.

SOCIETY OF APOTHECARIES' AWARDS

A largely attended soirée was given by the Master and Wardens of the Worshipful Society of Apothecaries of London on July 20, when the honorary freedom of the Society was conferred on Dr. Nigel Loring, apothecary to the Household of H.M. The Queen, and the gold medal in therapeutics was presented to Dr. E. Lester Smith in recognition of his work on vitamin B_{12}. In conferring the freedom the MASTER (Dr. H. S. MORLEY) referred to the long association between the Society and the apothecaries to the sovereign or to the royal household. The apothecary to James I, Mr. Lownes, by his action against a fellow member of the Society for malpractice, led indirectly to the granting to the Society of its charter by the King. Dr. NIGEL LORING, in acknowledging the honour done to him, gave some information about his predecessors which he had gathered from the archives of the Lord Chamberlain. The first apothecary to the Crown was appointed in 1345, when Edward III was taken ill in Scotland. It was not apparently a serious illness, for the King lived 32 years longer, to the age of 65, but the apothecary received a pension of sixpence a day for life, which was not munificent, even allowing for the different value of money. Henry VIII appointed an apothecary to look after his daughter, the Princess Mary. Charles II appointed two apothecaries, who first appeared in the list under the name of surgeons, but two years later were described as apothecaries—an indication not so much of change of function as of promotion, because in those days the surgeon was looked upon as a technician and the apothecary ranked above him. Two apothecaries were also appointed at the end of the reign of George II, but by that time the surgeons had risen in precedence and the apothecaries had fallen slightly.

The MASTER, in presenting the Society's gold medal to Dr. Lester Smith, remarked that the Society had always taken a great interest in the science of therapeutics. Formerly it had two silver medals for work in this field, but they fell into desuetude, and in 1925 it was decided to award one gold medal. A new design was made, with, on one side, the head of Galen, and on the other a lady representing science instructing a youth at her side in the properties of herbs. Former recipients of the gold medal included W. E. Dixon, Gowland Hopkins, Frederick Banting, Howard Florey, and Henry Dale. He called upon Sir Lionel Whitby, also a gold medallist, to give the citation of the work of Dr. Lester Smith. Sir LIONEL WHITBY said that Dr. Lester Smith had spent the whole of his working life in the laboratory. His early work was on cholesterol and on vitamin concentration, and he was concerned with attempts to prepare extracts for the treatment of pernicious anaemia. During the war he carried on important and successful work in connexion with the production of penicillin. After the war he resumed his researches, which could then be accelerated owing to the new knowledge, and in 1948 he prepared two red pigments which were found to be highly active in pernicious anaemia. Although they were considerably concentrated they were not at that time the actual pure material. Lester Smith's work was an excellent example of the pattern which should be followed in medical research and therapeutics. He had played an important part in leading up to the final isolation of the crystalline vitamin B_{12}, a discovery which had opened up enormous possibilities for studying metabolism and general nutrition, and was interesting alike to the medical specialist and to the scientific agriculturist concerned in the production of certain forms of animal protein. Dr. LESTER SMITH, in thanking the Master and Wardens, said that an award such as this could not properly be given to an individual. He was conscious of the fact that he had built on foundations laid by his predecessors, and that he owed much to his colleagues and to the whole laboratory in which he had worked.

Nova et Vetera

ROYAL HOSPITAL AND HOME FOR INCURABLES

This week the Royal Hospital and Home for Incurables, Putney, celebrates its centenary. Its foundation was due principally to the efforts of the Reverend Andrew Reed, a nonconformist minister and pastor of Wycliffe Chapel, New Road, Stepney. Reed actively engaged in philanthropic work for nearly 50 years. In 1813 he founded the London (Royal) Orphan Asylum, in 1827 the Infant Orphan Asylum, in 1844 a second orphanage, and in 1847 the Asylum for Idiots. His last great philanthropic effort was on behalf of incurables, of whom large numbers were being discharged from hospitals. Preliminary meetings were held at the London Tavern, Bishopsgate Street, on July 13 and 20, 1854, and permission was obtained for a public meeting at the Mansion House. This meeting took place on July 31 with the Lord Mayor presiding.

Reed submitted rules for the proposed hospital, which was "intended for the relief of men and women over the age of 30 who are hopelessly disqualified for the duties of life by disease, accident or deformity, and who are considered, after careful examination, to be beyond the likelihood of cure."

Among the members of the first board of directors were William John Little, the specialist on diseases and deformities of children, and John Conolly, who played an important part in the early history of the British Medical Association, particularly in the founding of the Metropolitan Counties Branch in 1852,[1] and who is best remembered for his introduction of humane methods of treatment at Hanwell Asylum. Little became physician to the new hospital.

During its first year the hospital received £1,874 (including a single donation of £1,000) and disbursed most of this. In 1953 income was £106,000 and expenditure £121,000. Up to 1947 income always exceeded expenditure, but since then the position has deteriorated. The hospital has remained a free and voluntary body outside the National Health Service. In order to ensure its continuance an appeal was recently launched by its president, the Duke of Devonshire, by which it is hoped to raise £100,000.[2] At present the hospital cares for 260 resident patients and gives small annuities to 250 pensioners living in their own homes. Future plans include admission of a few patients able to pay for part or the whole of their maintenance.

[1] Moody, J. A. (1954). *British Medical Journal*, 1, 997.
[2] *British Medical Journal*, 1954, 1, 529.

Correspondence

Obstetric Anaesthesia

SIR,—The illuminating article on the "Risk from the Aspiration of Vomit during Obstetric Anaesthesia," by Dr. R. B. Parker (*Journal*, July 10, p. 65), should induce serious thought in the minds of obstetricians, anaesthetists, and general practitioners, and provoke careful consideration of the anaesthetic procedures at present adopted. Indeed, it invites suspicion, if not condemnation, of methods which, though in general use, result in occasional deaths from such a cause during forceps delivery.

It is of particular significance that, as Dr. Parker demonstrates, the risk is associated with aspiration of both liquids and solids, and it is undeniable, as he points out, that so far from fluid being withheld during labour "the consumption of liquid is often encouraged" and with good reason. Solid food also is often not withheld, since, as I have pointed out before (*Journal*, February 13, p. 396), "indications for forceps delivery frequently arise unexpectedly." It is probably true to say that in respect of liquid or even solids few patients in labour are properly prepared for general anaesthesia in forceps delivery. What then is the answer?

Dr. Parker points out the advantages of purely local analgesia, but it seems unlikely, for various reasons, that this will become widely adopted at present, at any rate. He mentions certain preventive measures such as restriction of fluids, the stomach tube, tilting tables, mechanical suckers, laryngoscopes, bronchoscopes, and so forth, but, if he will allow one constructive criticism, he has omitted the one and only preventive measure which can and does render unnecessary all these precautions, and that is the abandonment of the lithotomy position in favour of the lateral position for forceps delivery. As I have said, "after more than 30 years of experience in the lateral position, it is quite inconceivable to me that fatalities from this cause would occur in that position," for the patient is *already in the position* into which she is eventually turned if respiratory obstruction occurs and any vomit just shoots into the bed to the dismay of the nurse and the delight of the anaesthetist. It is not easy, on the other hand, indeed it may be impossible, to extricate with sufficient speed a patient from the lithotomy position if vomiting occurs, however expert and agile the anaesthetist may be.

It is reasonably clear that the cases reported from the Birmingham Maternity Hospital were all delivered in the lithotomy position, except Case 1, which was a caesarean. In the series of fatal cases from inhalation of vomit reported by Professor T. N. A. Jeffcoate (*Journal*, October 31, 1953, p. 951), I succeeded in eliciting the fact that all were delivered in the lithotomy position. In a fatality from this cause at Cheltenham recently the patient was in the lithotomy position.

It may be that in a matter of this kind general practitioners who in their humbler way often have had to act as obstetrician, or as anaesthetist, and not infrequently as both, may be able to look at this important matter from a wider angle. At least, I know that many agree with me on this subject. If a fatality occurs it is the anaesthetist who comes in for the odium thereof, whereas it may well be that the obstetrician is the real villain of the piece, and yet how many anaesthetists, however they may feel, would have the courage to protest to the obstetrician that in anaesthetizing an ill-prepared patient in the lithotomy position they are subjecting the patient to a definite and unnecessary anaesthetic risk? That the matter is a grave reflection both on obstetricians and anaesthetists is shown by the analysis of Hingson and Hellman,[1] where nearly half the maternal deaths under anaesthesia were due to aspiration of vomitus."

It is obvious that all is not well with the teaching of obstetrics, for a student taught to put forceps on in the lithotomy position will almost certainly continue to do so in later practice, and so fatalities of this kind are likely to increase still further in the future, as those who use the lateral position are probably slowly diminishing in number. In all seriousness, is there not a solid case for the teachers of obstetrics (for with them the solution lies) to consider whether a return to the sanity of the lateral position might not go a long way towards the prevention of these avoidable calamities? For few things are so tragic as a maternal death.—I am, etc.,

Mill Hill, N.W.7. A. H. MORLEY.

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SIR,—To Dr. R. B. Parker's plea (*Journal*, July 10, p. 65) for the wider use of local analgesia in obstetrics might be added that of Professor Jeffcoate (1953), who stated that the risks of general anaesthesia constitute the chief reason for advocating the use of local analgesia for all easy low-forceps extractions.

The mortality rate of local analgesic agents is extremely difficult to assess (Hewer, 1953), but the occurrence of idiosyncrasy or overdosage is well known and may lead to convulsions, circulatory collapse, and death. Ideally a test dose of the drug should be given beforehand in every case, and the needle must be kept moving during the injections. Premedication needs to be liberal (Nixon and Ransom, 1951) and should include a short-acting barbiturate (Lundy, 1942). It is apparent that there are objections to the wholesale adoption of local analgesia for easy low-forceps extractions. But, even if these be ignored, what of the difficult forceps case?

Intrathecal and caudal analgesia can have serious complications and sequelae; general anaesthesia remains for consideration. Jeffcoate (1953) states that the danger of inhalation asphyxia has increased at the Liverpool Maternity Hospital since the introduction of modern anaesthetic agents—presumably thiopentone and relaxants—and Dr. Parker has reiterated the fatal nature of the "acid aspiration syndrome," and inhalation asphyxia associated with gas, oxygen, and ether.

Clearly safety can only be achieved during the induction and recovery phases if the stomach is empty. This state is not necessarily achieved by withholding food and drink, as pointed out by Nixon and Ransom, for the stomach may fill with fluid in the presence of the ileus which sometimes occurs during labour. The head-down tilt cannot be relied on to prevent aspiration of stomach contents (Morton and Wylie, 1951; O'Mullane, 1954); therefore there seems to be no choice for the anaesthetist but to pass a full-sized stomach tube, reluctant though he will be to cause further distress to the labouring woman.—I am, etc.,

Thornton Heath. E. GODWIN.

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Cardiac Infarction and Peptic Ulcer

SIR,—The association of these conditions in two cases reported by Dr. P. S. Elias (*Journal*, July 10, p. 103) is in parallel with the experience at Whittington Hospital, where gastric or duodenal ulceration has been found in 37 out of 569 consecutive cases of cardiac infarction (6.5%). Acute haemorrhage occurred in 13 of the patients and perforation of the ulcer in three. If it can be accepted that stress, in its widest sense, plays any part in the pathogenesis of either condition the figures are not surprising. But, surely, the importance of recognizing this not uncommon situation is that anticoagulant drugs should be withheld in such cases. Bleeding does not invariably occur, as Dr. Elias writes, but it is always a possibility and may be disastrous.—I am, etc.,

London, N.19. H. E. S. PEARSON.

Varicocele and Male Subfertility

SIR,—Dr. J. K. Russell's article (*Journal*, May 29, p. 1231) on the above subject is interesting.

Dr. H. A. Davidson's theory (*Journal*, June 12, p. 1378) as to the cause of poor spermatogenesis is ingenious. However, I think Dr. H. S. Russell (*Journal*, July 24, p. 241) is right in deprecating the operative removal of varicoceles for this condition.

Forty years ago radical operations for varicocele were performed frequently in answer to demands of entrants to the Services—a demand that is no longer made. Experience proved that the results of operation were not always satisfactory, wasting or the development of hydrocele of the affected testis being not uncommon. I think it is impossible to remove a varicocele of any size without damaging the spermatic artery. Such interference with the vascular supply of the organ cannot be expected to improve its nutrition.—I am, etc.,

Faversham. MAX PAGE.

SIR,—I was interested to note from correspondence in your columns that research work performed five years ago on the thermoregulatory function of testicular blood vessels in the experimental animal[1] is now being applied to observations on human spermatogenesis. Dr. H. A. Davidson's letter (*Journal*, June 12, p. 1378) describes the untoward effect of varicocele on spermatogenesis as being due to its effect as a radiator, counteracting the local thermoregulatory mechanism. Species differences in the degree of convolution and calibre of the testicular artery and its relation to the veins of the pampiniform plexus[2] would appear to account in some measure for observed differences in abdomino-testicular temperature gradient.[3] Experiments on dogs, rams, and goats also indicate that the close relation of the pampiniform plexus of veins to the testicular artery is well adapted to bringing about preheating or precooling of arterial blood flow to the testis.[4] This mechanism allows for regulation of intra-testicular temperature on exposure of the scrotum to environmental temperatures higher or lower than that of the testis itself. The adverse effect of increased temperature on spermatogenesis in both the experimental animal[4] and man[5] is well known, but it is not generally realized that low temperature is just as important. Recent experiments[6] have shown that temperatures of −6 and −8° C. when applied directly to the rat testis for one hour cause destruction of all spermatogenic cells with no evidence or possibility of regeneration, whilst a temperature of −10° C. applied to the scrotum for one hour produces severe spermatogenic damage, in which the majority of spermatogenic cells are necrotic and only a few survive. These changes are caused by ischaemia occasioned by the low temperature. It is possible that less cooling of the human testis than in the rat may be effective in producing spermatogenic damage.

Although a varicocele may well act as a "radiator" in disturbing the thermoregulatory capacity of testicular vessels, the mechanism of its action may be belied by this term. The dilated veins of the varicocele would present an increased surface area to the arteries of the spermatic cord and thus permit more extensive heat exchange between arteries and veins, as well as radiating heat to the exterior through the scrotal skin. In a hot environment, if the venous temperature is initially below that of the artery, it rises more rapidly than that of the artery and may reach or surpass it[1]; the thermal gradient is therefore reversed, and the heat flow from vein to artery. A varicocele would facilitate this heat transfer, and the result would be a rise in intratesticular temperature. In man such a rise of about 2° C., if sustained, would be adequate to effect damage to spermatogenic cells, and could be brought about by excessive insulation of the scrotum over long periods—for example, by thick underwear and the protective devices used by athletes—or *repeated* bathing at high temperatures, as already suggested.[7] Dr. Davidson's observations on the semen picture in cases of hydrocele and varicocele, and in persons wearing scrotal supports, are therefore of great importance, and it is to be hoped that correlated measurements of intratesticular temperature and the anatomy of the testicular vessels may be undertaken in such cases.

The optimum point of ligation of the testicular veins in operations for varicocele has already been discussed at length.[8,9] The danger to arteries supplying the testis[9] and epididymis[10] in this operation has also been thoroughly investigated. Anatomical principles suggest that the vasal artery (artery to the vas, deferential artery), although of minor importance for the vascularization of the testis, may not alone supplant the testicular artery, as suggested by Mr. J. Johnston Abraham (*Journal*, June 26, p. 1498). The human testis is, however, well furnished by having a direct anastomosis of the testicular artery with the vasal artery and, in two-thirds of cases, a functional anastomotic connexion with both vasal *and cremasteric* arteries. The sum of the diameters of these two arteries is at least equal to the diameter of the testicular artery in one-third of cases. Such factors are undoubtedly concerned in the variability of post-operative sequelae to the testis. Recent investigations[10,11,12] have also stressed the vulnerability of arteries supplying the epididymis; these vessels lie superficially in the spermatic cord and may arise from the testicular artery near the superficial inguinal ring. Experimental arterial ligations which occlude the vessels supplying the caput epididymis in the rat produce epididymal necrosis, obstruction of the vasa efferentia and swelling of the testis followed by atrophy.—I am, etc.,

Liverpool. R. G. HARRISON.

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Antenatal Care and the Local Health Authority

SIR,—There will be widespread and heartfelt agreement with the contention of Mr. T. F. Redman and Dr. S. C. B. Walker (*Journal*, July 3, p. 41) that "there should be firm links between the antenatal clinic and the hospital, so ensuring continuity of medical policy throughout the antenatal period, labour and the puerperium to the post-natal visit." They are to be congratulated on their efforts to realize this at Bristol. It is a pity, however, that they have not appreciated that this applies at least as much to "antenatal and relaxation sessions" as to any other part of treatment. Whether or not one agrees with such sessions is another question. But if they are to be carried out at all it might as well be with the intention of giving as much help as possible. And this aim is never achieved without those "firm links" being forged especially strongly. It seems a pity that "relaxation sessions" should be thrown to the local health authority as a sort of consolation for its dwindling responsibility.—We are, etc.,

W. C. W. NIXON.
London, W.C.1. SHILA G. RANSOM.

The Place of the Baby

SIR,—All will have been horrified by the death of 13 babies following a maternity home fire in April despite the heroism of the night sister. But what is even more horrifying is the fact that this tragedy could occur at all. Had these babies been in their rightful place—beside their mothers—they would never have been left in a smoke-filled room.

Most mothers do not find out that they are not to have their babies with them until too late. Those that do find out in time, if they have the courage, may mention the subject to be met either with blank disbelief or with ridicule,

and their wishes are completely overridden unless they can afford to make alternative arrangements. And how many can do this nowadays?

If this tragedy can do something towards abating this practice it will not have been completely in vain.—I am, etc.,

London, S.E.19. MICHAL M. M. TACK.

Cyanacetic Acid Hydrazide

SIR,—Valdecasas *et al.*,[1] Hartl,[2] and Scheu[3] have described the antituberculous properties of cyanacetic acid hydrazide ("cyanazide," "reazide") and claimed that it might be of value in the treatment of tuberculosis. During the last few months we have been investigating the activity of this drug, both in the test-tube and in various experimental animals. Though our experiments are not yet complete, our results suggest that caution should be observed in using this drug clinically. In particular we have found that (1) the *in vitro* and *in vivo* activity of cyanacetic acid hydrazide is substantially less than that of isoniazid, although there is little difference between the two drugs in their acute and chronic toxicity for mice; (2) strains of *M. tuberculosis* which have become resistant to isoniazid, either *in vitro* or in patients, usually show increased resistance to cyanacetic acid hydrazide; and (3) a strain of *M. tuberculosis* made resistant to cyanacetic acid hydrazide *in vitro* is also resistant to isoniazid.

Consequently it appears that the indiscriminate use of the new drug may well have the danger of building up a population of patients with isoniazid-resistant strains. This danger might be particularly great if the drug were used alone.—We are, etc.,

MARGARET BARNETT. R. KNOX.
S. R. M. BUSHBY. J. M. ROBSON.
R. GOULDING.

The Wellcome Research Laboratories, Beckenham, Kent, and Guy's Hospital Medical School, London.

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Cortisone and Aspirin in Rheumatoid Arthritis

SIR,—The report of the Joint Committee of the Medical Research Council and the Nuffield Foundation on the comparison of cortisone and aspirin in early cases of rheumatoid arthritis (*Journal*, May 29, p. 1223) and your leading article on the same subject (p. 1249) prompt me to refer to some of our observations on salicylate. It now seems possible to include early rheumatoid arthritis among the conditions affected by this drug.

The fact that the therapeutic spectrum of salicylates agrees fairly well with that of cortisone suggested investigations of this similarity years ago, and many workers have demonstrated the participation of the adrenals in different salicylate actions in animals. Without attributing a specificity to our observations, we described,[1 2] among others, that (1) high doses of salicylate remarkably inhibit the otherwise greatly increased permeability of the rat hind-paw induced by testicular extracts containing hyaluronidase; (2) this inhibiting effect of salicylate is lost if the adrenals, or their active constituents, are absent; and (3) the adrenal medulla also seems to participate in this acute response in the investigated range.

There are, however, other factors which influence the development of this acute, protein-rich oedema, amongst these the local reactivity of the tissues of the hind-paw, circulatory factors, etc. Dehydration, as suggested by Reid *et al.*,[3] seems also to merit more attention.

In the light of the available observations we attempted to prove the significance of adrenal participation in the salicylate action in humans. With the high dose of 6–9 g. salicylate orally, within a few hours significant eosinopenia was elicited in 16 out of 23 cases, whilst smaller doses (3–5 g.) remained ineffective in 22 out of 26 cases. The daily excretion of urinary cortisone-active material, however, as determined by the bio-assay of Cope,[4] was unaltered even in the high dose group.[5] Most authors seem to agree with these experiments. The question arises, however, whether the fact that the urinary excretion of cortisone-active material fails to increase during salicylate therapy is enough to allow us to conclude that adrenocortical mechanisms are of no importance in the action of salicylates. I think that this is not the case. In agreement with Selye[6] we wrote[7] that it is possible to influence permeability if what would be otherwise insufficient amounts of salicylate are combined with corticotrophin in the normal, or with cortisone in the adrenalectomized animal, under experimental conditions in which both corticotrophin and cortisone alone were ineffective. These animals, as well as those in Selye's experiments, seem to be conditioned for the effect of active corticoids.

A further complicating factor was also mentioned.[5 7] The remarkable increase in metabolism may be responsible for the failure to demonstrate increased amounts of substances with cortisone-like activity in the urine of salicylate-treated humans. In fact, Cochran[8] recently suggested that the metabolic increase played a major role in salicylate action. High increases in oxygen consumption, however, were not accompanied by an inhibiting effect upon oedema formation if young animals (weighing under 100 g.) were used in our salicylate experiments. Further, Donhoffer *et al.* observed (personal communication) that salicylamide, which is said to be therapeutically active, often diminishes oxygen consumption in the rat.

With regard to plasma 17-hydroxycorticosteroids, at plasma salicylate concentrations greater than 25 mg. per 100 ml., Ely *et al.*[9] frequently observed increases in the 17-hydroxycorticosteroids, although the English group[10] found unaltered levels. Further work is, therefore, needed to decide both the role of metabolic increase in humans and the state of plasma 17-hydroxycorticosteroids at high salicylate concentrations.

The recent work of the Salt Lake City school[11] shows that the 17-hydroxycorticosteroid concentrations observed in the early days of salicylate intoxication are comparable to those observed during A.C.T.H. therapy (20, 5–48, 2 μg. per 100 ml.). We, however, learned from our permeability experiments that results of acute trials could only be transferred to the prolonged treatment with reserve.

In conclusion, the explanation of the therapeutic action of salicylate, whether connected with cortisone or not, remains unsolved. It is true that its therapeutic action could hardly be explained with a cortisone mechanism alone. It is true also that smaller salicylate doses, without any demonstrable influence upon adrenocortical or adrenal mechanisms, are often said to be active therapeutically, and there appears to be no explanation for this. As far, however, as the permeability mechanism in the rat's hind-paw permits any conclusion, salicylate—at least in a range and in the early days of its administration—seems to act in the presence of, but not exclusively through, the adrenals, including also the adrenal medulla.—I am, etc.,

Szeged, Hungary. E. KELEMEN.

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Snoring

SIR,—In the *Daily Telegraph* dated July 7 the report of the meeting of the British Medical Association at Glasgow stated that its members are not aware of the cause of or cure for snoring.

Many of those members of the dental profession who practise "bite-rehabilitation" ascribe snoring to malpositioning of the jaws. It is my experience that over the

past ten years the majority of persons so affected have this condition of the jaws. This in turn causes a cramped positioning of the tongue, and in consequence interferes with respiration. If the jaws of such persons are reorientated—a simple painless procedure—by means of splinting to a correct physiological relationship, the respiration is invariably improved, and, in the vast majority of cases, snoring ceases.—I am, etc.,

London, W.1. RAEL JACOB.

Heart Cases on Cruises

SIR,—Recently I went on a cruise to the Mediterranean and was appalled that two people died from heart complaints, one of whom was buried at sea. Another heart case had to be put ashore at Naples for hospital treatment. In addition, at least five other patients spent most of the cruise in the ship's hospital, of whom four were heart cases and one had a lung condition. Obviously, patients so severely ill are a great worry and anxiety to the ship's doctor, and depressing to other passengers. The doctor informed me that investigation has shown in many such instances that heart cases have been advised by their doctors to go on a cruise for the benefit of their health, but what of the danger and the sorrowing relatives on board?—I am, etc.,

London, N.W.8. BERNARD E. MYERS.

"Sulphatriad" Anuria

SIR,—Dr. H. R. E. Wallis (*Journal*, July 10, p. 102) has attempted to resuscitate the bogy of sulphamerazine's toxicity. This topic had been allowed to rest in peace since 1952. The reported cases of haematuria and crystalluria had then all followed gross overdosage, and one had hoped that by now the recommended doses would be in general use. I have used sulphamerazine whenever a sulphonamide has been indicated since it was introduced, and have never encountered toxic effects. I felt that the law of averages was perhaps catching up with me a week ago, when I saw a child, after four days' treatment of a streptococcal pharyngitis, passing scanty and bloody urine. Inquiry soon elicited, however, the fact that I had given this particular child oral penicillin. Sulphamerazine will continue to be used in my practice, largely because of its ease of administration to small children, who only require 12-hourly dosage, a great advantage to the already harassed mother.—I am, etc.,

Bushey Heath, Herts. D. G. WILSON.

Guillain–Barré Syndrome

SIR,—In his interesting article on the Guillain–Barré form of polyneuritis (*Journal*, July 10, p. 84) Dr. Idris Jones states that the principal reason for reporting the cases is "the observation, not hitherto recognized, that in the early stages the deep tendon reflexes are exaggerated." C. P. Symonds, writing on polyneuritis in the fifteenth edition of *Taylor's Practice of Medicine* (1936), states that "the tendon jerks in the earliest phase of the disease are temporarily exalted." It would appear, therefore, that this clinical observation has been made previously.—I am, etc.,

Dewsbury. GODFREY B. TAIT.

Sesamoid in the Gastrocnemius

SIR,—I would like to report an unusual case of a swelling in the popliteal fossa.

A man, aged 29, presented with pain and swelling at the back of his left knee for the previous six weeks. The pain radiated from the back of the knee down to the lateral side of his ankle. Nine months before the patient had strained his lumbo-sacral region and had had slight pain radiating from there down to his left knee since, and worse over the previous six weeks.

A tender hard immobile swelling about half an inch (1.25 cm.) in diameter was found in the lateral angle of his left popliteal fossa over which the lateral popliteal nerve could be rolled, causing tingling down its distribution. No motor or sensory loss was detected in the distribution of the nerve. *X*-ray examination of the knee showed a sesamoid bone in the lateral head of the gastrocnemius, but no other abnormality. In the right knee there were no clinical features, but there was a sesamoid bone in the lateral head of the gastrocnemius, slightly smaller than on the left side. *X*-ray examination of his back showed slight diminution in the lumbo-sacral interspace.

After excising the left sesamoid bone, there was no further pain in his left knee, or radiating down to the ankle, but numbness had developed for about two inches (5 cm.) below the incision scar. The pain in the back and thigh, although still present, is less marked. It was concluded that the sesamoid bone had been pressing on the lateral popliteal nerve.

No previous reference to such a case could be found in the library of the Royal Society of Medicine. I am grateful to Mr. J. Thompson Fathi for permission to publish the details of this case.—I am, etc.,

London, E.15. HUGH M. HADLEY.

Back to the Barber's Pole

SIR,—Mr. P. R. Allison's letter (*Journal*, July 3, p. 45) suggests that the institution of pre-anaesthetic clinics is, for the surgeon, a step "back to the barber's pole." He maintains that all pre-operative treatment should be carried out by the surgeon and asks what confidence a patient will have in a surgeon who advises an operation, if, at another clinic, an anaesthetist gives contrary directions. Which is the best system for the general surgical patient?

Personally, I am grateful to colleagues who give me expert advice in their special fields, particularly in difficult borderline cases. Not least, I value the opinion of the anaesthetist who is going to be responsible for the patient during the operation, and am grateful to him if he sees the patient as an out-patient. If he thinks further investigations or preparation wise, these can then be carried out without delaying the patient's admission or operation.

For the integration of investigations, opinions, and recommendations the patient returns to the surgeon, who is now in the best possible position to advise his patient. I have yet to meet a case referred by me to the pre-anaesthetic clinic which the anaesthetist has refused to undertake. When this position arises, it will be a matter for mutual consultation between colleagues. Under Mr. Allison's system, the surgeon would already have decided the issue at stake, the anaesthetist being consulted only at his pre-operative visit. This, in my opinion, is not in the patient's best interest, and shows a lack of courtesy to the anaesthetist.

Mr. Allison's relegation of the anaesthetist to a subsidiary role is reminiscent of the days when the surgeon even directed what form of anaesthesia was to be given. It is a step back, not to the barber's pole, but to the one-man band beloved of the children of 50 years ago. This may well have had musical merit, but is in no way to be compared with a well-conducted orchestra.—I am, etc.,

London, W.1. ANDREW MONRO.

Standard of Anaesthetics in Britain

SIR,—Mr. A. Dickson Wright is no doubt heartily tired of the controversy which his recent remarks have aroused. His suggestion (*Journal*, June 12, p. 1380) that an instrument be made which will give instant warning when the heart falters or stops is of value, for it is impracticable to palpate the pulse continuously in a series of patients throughout the six or eight hours which the anaesthetist spends in an operating theatre. Moreover, it is now over twenty years since Hill[1] pointed out that dangerous cardiac arrhythmias can occur during anaesthesia which are not detectable by ordinary clinical methods. A two to one heart block is not uncommon, and the true heart rate may be double that recorded by the anaesthetist. Hill's observations were confirmed by Kurtz, Bennett, and Shapiro[2] two years later and by several investigators since. A cathode-ray electrocardiograph would probably give warning of dangerous ventricular rhythms, but a type suitable for routine use is not available. May I suggest the use of a simple "pocket" instrument[3] which I have used for the last five years? It is now being

made by K.D.G. Instruments Ltd., Purley Way, Croydon. It has the advantage that disappearance or irregularities of the pulse are obvious at once and no special skill is required to fix the pick-up to wrist or temporal artery. It has the further advantage that changes in blood pressure or cardiac irregularities due to irritation of the peritoneum, rough handling, or traction on viscera are plainly visible to onlookers. I do not share the satisfaction of Dr. Cope with the modern anaesthetic machine, and am unable to see any important improvement in the last 15 years. I know of no physician who administers a series of dangerous drugs of the relative composition of which he has only a vague idea—yet this is what the anaesthetist is forced to do, for on no gas machine, British or American, is there any means of indicating the exact gas or volatile anaesthetic concentration which the patient is breathing.

Carbon dioxide poisoning, which is not clinically obvious until the gas reaches a concentration of 7%, is another danger ignored by the manufacturers, who appear to be more interested in the appearance than the function of their products. I could enlarge on this theme, but your space can be put to better use.—I am, etc.,

Jamaica. V. J. KEATING.

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SIR,—I have been most interested in the correspondence dealing with Mr. Dickson Wright's remarks concerning anaesthesia and cardiac arrest made before an audience largely composed of American surgeons. In his letter (*Journal*, June 12, p. 1380) he writes: "For the present, the price of safety must be perpetual vigilance, until some certain machine arrives to tell us (*a*) when the heart is wavering and (*b*) the moment it stops."

Known as a "cardioscope," such a machine does in fact exist and has been known to many American surgeons for perhaps two years or more. This machine, which is made by the Cambridge Instrument Co., Inc., of New York, can be fitted to ring a bell the moment dangerous bradycardia or arrest occurs.—I am, etc.,

Cooperstown, N.Y R. A. C. HERRON.

Suicidal Attempts in Alcoholics

SIR,—Dr. I. R. C. Batchelor, in two interesting recent articles,[1 2] refers to the relationship between alcoholism and suicide. Among 200 cases of attempted suicide he found 43 (21.5%) "pathological, excessive drinkers"; most of these, however, suffered from "psychopathic" (19) or "depressive" (15) states. Only five were "chronic alcoholics," and he concludes that the "chronic alcoholic" does not typically commit suicide.

It may be interesting, in this connexion, to mention some figures relating to the frequency of suicidal ideas and suicidal attempts among alcoholics obtained by questioning patients admitted to Warlingham Park Hospital during the last one and a half years because of "alcoholism" (as defined by the W.H.O. Alcoholism Subcommittee[3]). Of 75 male alcoholics, 40 stated that at some time or other they had thought that it would be best for them to be dead, 24 (32%) had contemplated suicide more earnestly, and 19 (25.3%) had actually attempted suicide. Among 28 female alcoholics the corresponding figures were: 10 with death wishes; 8 (28.6%) had contemplated committing suicide, and 5 (17.8%) had attempted it. The great majority of these patients would be classifiable under the term "chronic alcoholic" as employed by Batchelor, as their alcoholism was the central feature of their abnormality; but there were 10 psychopathic personalities among the 19 men who attempted suicide, and 4 among the 5 female patients. Most of the remaining patients who had attempted suicide were neurotics with depressive features.

It appears from these figures that in the history of our "alcoholic" patients suicidal ideas were common and suicidal attempts not infrequent. The alcoholic's compulsive drinking leads inexorably to a gradual disintegration of all aspects of his personality and of his social life, and he seeks temporary oblivion from his psychological pain or some fleeting happiness. Underlying aggressive tendencies present in the alcoholic against himself as well as against others frequently find release whilst he is under the influence of drink. Thirty-one of our male alcoholics and 14 of the female alcoholics stated that they had acted in a way dangerous to themselves or to others whilst intoxicated. In time, however, alcohol ceases to give the alcoholic the inner peace he is looking for; difficulties arising out of his drinking behaviour become superadded to the ones which originally prompted him to seek relief in drinking; and the gradual self-destruction by alcoholism is then replaced by acute acts of self-destruction, permanent oblivion is looked for instead of temporary oblivion, and, instead of looking for "some way out of the prison house of reality back to the Golden Age,"[4] he tries to escape from his prison for ever. For the alcoholic merely to stop drinking, therefore, in the great majority of cases is not enough, although, of course, this is absolutely essential, and will in itself lead to the disappearance of many "secondary" difficulties. He has to learn to find better means to overcome his difficulties than by gradual or sudden self-destruction, and to adopt a new attitude towards life, as set out, for example, in the programme of Alcoholics Anonymous.—I am, etc.,

Warlingham, Surrey. M. M. GLATT.

REFERENCES

1 *British Medical Journal*, 1954, **1**, 1342.
2 *J. ment. Sci.*, 1954, **100**, 451.
3 Alcoholism Subcommittee Second Report, *Wld Hlth Org. Techn. Rep. Ser.*, 1952, No. 48.
4 Trotter, W. (1916). *Instincts of the Herd in Peace and War*. London.

Intramuscular Iron

SIR,—A patient of mine who had been losing blood from bleeding haemorrhoids was found to have, on June 15, 1954, a haemoglobin of 50%. Ferrous sulphate oral therapy was started, but on June 18 the haemoglobin was still only 50%. It was decided to augment the ferrous sulphate tablets with intravenous iron, so as to raise the haemoglobin value more quickly.

Unfortunately, for technical reasons, it was not possible to give the iron intravenously, and the same preparation ("ferrivenin") was injected instead into the gluteal muscles as an intramuscular injection. 2.5 ml. was given twice a week with an amazing response. A blood examination performed on July 6 showed the haemoglobin to be 86%. In spite of an intravenous preparation being used intramuscularly, pain and discomfort have been transient and minimal, with no after-effects whatever.—I am, etc.,

London, S.W.3. DAVID THOMAS.

Smoking and Lung Cancer

SIR,—In his statement about the relationship between smoking and cancer of the lung, the Minister of Health insisted that no alarmist conclusions should be drawn from his words. Unfortunately, millions who have smoked for 10 to 30 years are irritated and alarmed. As a practitioner and surgeon who has studied this problem for 30 years, I feel that smokers should realize that the conclusions of the Standing Advisory Committee on Cancer and Radiotherapy are based on evidence that would hardly satisfy the legal mind. Of the two conclusions, the first was based on statistics and the second on the result of experiments. But statistics are so uncertain that men of international repute have expressed at least three contradictory views—that is, that the total cancer mortality rate is stationary, that it is decreasing, that it is on the increase. The upholders of the first two views argue that the increase is not genuine but due to *x* rays, early operation, and better diagnosis which has substituted cancer for old age as a cause of death.

But what is seldom stated is that, even if the mortality tables show an increase from cancer of the lungs, that increase is counterbalanced by a decrease in cancer of the mouth, tongue, stomach, and oesophagus. For in spite of the different distribution of cancer on the two sexes (58% of all female cancers are genital) the death rate for the two sexes is about equal. About 100,000 males and the same number of females die every year in U.S.A. And not only has the death rate from cancer of the lung increased but cancer of the prostate, for instance, which can hardly have any relationship to smoking, is constantly increasing. In the United States 18,000 deaths occur every year from cancer of the prostate. A similar shift in the distribution of cancer has been observed in females. If pregnancies increase, the proportion of cancers of the cervix uteri goes up from 44% to 84%, and cancer of the corpus uteri comes down from 56% to 16%, but in total cancer-incidence women who have never been pregnant are neither better nor worse off than women with one pregnancy. Married women may derive comfort from the fact that, if they have more cancer of the uterus, spinsters have more cancers of the breast. The distribution of cancer is constantly shifting from one organ to another but the total incidence of cancers remains about equal.

The second conclusion is based on experiments on mice and rats. Tar and many of its derivatives induce cancer of the skin, breast, and lungs. But tar is not directly responsible for these induced cancers, because an additional, still unknown, factor must be present before a cancer develops. Even if cancers could be induced in experimental animals, it would not provide evidence that smoking is the carcinogenic agent in man. Experimenters succeeded as far back as 30 years ago in inducing cancer of the lung and breast in mice. Such experiments have been going on for half a century and can lead no further. But to-day more than 100,000 tar derivatives are on the market as drugs. The nation is eating and drinking tons of such drugs every year. What evidence exists that this reputed increase in cancer of the lung is not due to the higher consumption of drugs derived from coal tar?

Finally, brewers and inn-keepers have a death rate from cancer three times as high as farmworkers or parsons, and evidence is accumulating that this is due to their higher consumption of alcohol. But the medical profession does not, so far, consider beer, wines, and spirits as carcinogenic agents.—I am, etc.,

London, W.1. K. BLOND.

The Role of Smoking in Bronchitis

SIR,—Dr. James Gregory writes (*Journal*, July 17, p. 175) that occupational factors were not considered in the group of patients that were studied for my article, "The Role of Smoking in Bronchitis" (*Journal*, June 26, p. 1473), and he wonders how many of these patients worked in dusty occupations.

The occupation of the patient was considered, but, as on analysis only 3 of 422 had an occupation in which they were exposed to dust or rapid changes of temperature (they were stokers employed looking after domestic furnaces in blocks of flats), this point was not included in the table of the incidence of factors, other than smoking, which are likely to lead to the development of bronchitis. The majority of the patients were of the white-collar worker class, and the remainder were doing light work in a non-dusty environment.—I am, etc.,

Aberdeen. K. N. V. PALMER.

Studies in Human Lactation

SIR,—In his letter (*Journal*, July 17, p. 171) Professor R. S. Illingworth has not only misrepresented my paper (*Journal*, June 19, p. 1410) but has also misquoted his own book.[1]

I made no reference to a vitamin deficiency of breast milk but to vitamin deficiency in breast-fed infants. There is, I suggest, a big distinction. The statement on page 54 of Professor Illingworth's book was not, as he says in his letter, that "a baby should not be taken off the breast because the mother or someone else says the breast milk looks watery." In the book the verb used was not "looks" but "is," again by no means the same thing. I mentioned not two quoted authors from the book but three, and although they did not occur in the same chapter they are nevertheless quoted in the same connexion—that is, as evidence that almost all women are capable of fully breast-feeding their infants.—I am, etc.,

Aberdeen. F. E. HYTTEN.

REFERENCE

[1] *The Normal Child*, 1953. Churchill, London.

Treatment of Idiopathic Hypercalcaemia

SIR,—In the excellent report (*Journal*, July 17, p. 165) of the discussion on the aetiology and treatment of marasmus in the Section of Child Health at the Annual Meeting in Glasgow, I was reported as saying, with regard to treatment of idiopathic hypercalcaemia, that "possible methods are to give a diet containing very little calcium or to increase calcium elimination, which could be done by administering chelating agents." In fact I stated that elimination might be attempted by the use of sodium ethylene-diamine-tetra-acetate (E.D.T.A.), but I added a warning about the difficulties. This method of treatment has, in fact, been attempted, but anyone intending to try it ought to know that the administration of the sodium salt in states of hypercalcaemia has not emerged from the experimental stage, and the use of this preparation can be dangerous.—I am, etc.,

London, W.2. REGINALD LIGHTWOOD.

Proposed Coat of Arms for B.M.A.

SIR,—As one who has for many years made heraldry a pleasant relaxation from the ardours of medical practice, may I add a few comments to the correspondence on the above subject?

The shield is a fine example of nobility and simplicity, both of which are features sought by the best heraldic artists. The lion passant is beautifully drawn, though the word "horned" in the blazon is surely a misprint for "armed." Your correspondent Mr. Edward Elmhirst (July 10, p. 102) should know that the lion must be "passant" and not "passant guardant," as a "lion passant guardant or" is the lion of England, which is an honourable augmentation not granted except by royal warrant.

Certain words in the blazon require revision. I feel that torse or wreath is preferable to twist, and the crest should be "on" and not "from" a wreath (or torse). The wreath is correctly depicted in the livery colours of the arms, but it would be more appropriately drawn to look like intertwined coloured silks rather than a short length of old rope or a twist of tobacco. It is to be hoped that no thought will be entertained to include a helmet on which to place the crest, for I can imagine few things more uncomfortable or incongruous than a serpent and a flaming torch borne on one's headgear.

The supporters are no doubt appropriate, though I can imagine our lay friends getting some amusement from the apple of Hippocrates and from the rather constipated facies of our illustrious forebears.—I am, etc.,

Priors Marston, near Rugby. GEORGE A. MACDONALD.

POINTS FROM LETTERS

Medical Directory

The Editor of the *Medical Directory* writes: The accuracy of the *Directory* depends on the return of the annual schedule which has recently been posted to members of the medical profession. Should the schedule have been mislaid I will gladly forward a duplicate upon request. The full name of the doctor should be sent for identification. Communications should be addressed to the Editor, *Medical Directory*, 104, Gloucester Place, London, W.1.

Obituary

HENRY PETERKIN, M.B., Ch.B.

Dr. Henry Peterkin, consulting aural surgeon to the Aberdeen Royal Infirmary, died in an Aberdeen nursing-home on July 12, aged 77 years.

Henry Peterkin was born on March 14, 1877, the son of an Aberdeen solicitor who was one time chairman of directors of the Aberdeen Royal Infirmary. He was educated at the Aberdeen Grammar School and Aberdeen University, where he graduated M.A. in 1896 and M.B., Ch.B. in 1900. After a year as house-surgeon he made two voyages to Australia as a ship surgeon, and then spent a year in Vienna studying diseases of the ear, nose, and throat. Returning to Aberdeen, he started in practice as an aural surgeon. In those days there was no department in the Infirmary for treatment of diseases of the ear and throat, but Peterkin was appointed, after a period of ill-health for over a year, as an assistant to the late Sir John Marnoch in the general surgical wards. Gradually the cases belonging to his specialty, then being dealt with by the general surgeons, were transferred to him, and in a few years he was appointed the first specialist with wards in ear, nose, and throat surgery in the north-east of Scotland. With characteristic thoroughness he built up a first-rate department and received recognition from the university by being appointed lecturer in these subjects—a position he retained until he retired in 1935. During the first world war he was a captain in the R.A.M.C. (T.F.) from 1915 to 1919, attached to the 1st Scottish General Hospital. For the last twenty years he lived in retirement in Edinburgh and Aberdeen, while increasing ill-health deprived him of most of his activities except his love of good literature.

R. R. writes: Henry Peterkin was a man of very distinctive personality. In appearance he was what we of the north-east call a "kenspeckle" figure—tall, erect, and always sartorially and professionally correct; practically always on foot—he never owned a motor-car—striding along with stately carriage between his house and nursing-homes and hospital. He was a man of few words, yet paradoxically he was probably the finest and most cultured public speaker in the medical profession of the north-east. His oration in presenting the late Sir Ashley Mackintosh with his portrait is still remembered as a masterpiece by all who heard it. He was a prodigious reader both of general literature and of medical works—it is even said he learned Italian specifically to read a treatise on the ear in the original language—and was quite an authority on Osler and his writings.

With one exception he was the last of his generation of medical teachers, and of that race of doctors who in their handling of their patients could afford to be oracular and dogmatic. I belong to a medical class which commenced its studies half a century ago, and Peterkin was the last survivor of our teachers. The final phase of his illness actually struck him when he was in course of preparation of a message to our class reunion—a message, he said, that would come from the dead, as he would not survive our meeting. His friendship was not given lightly, but once given was staunch and enduring and displayed a loyalty which marked every aspect of his life—a loyalty to his friends, to his profession, and to the loftiest ideals inspired by that profession.

Dr. W. P. J. DUNSMORE died at his home at Skegness on June 18 at the age of 51 after six months' illness. Born on December 25, 1902, William Patrick Joseph Dunsmore was at school at Bradford and at Xaverian College, Manchester. He received his medical education at Dublin, qualifying L.R.C.P. and S.I. in 1933. He practised mostly in Yorkshire and the Midlands, and for the last few years had acted as locumtenent. Recently he had been severely handicapped by ill-health, and he fought hard to overcome this, keeping to the end his usual kind, patient, and courteous attitude to patients and friends. He married Miss Violet Taylor in 1952. They met while she was nursing at the Grace Swan Memorial Hospital, Spilsby, Lincolnshire.—M. R. P.

Dr. KENNETH MULLEN died early this month at Southsea after a long illness. He was born on June 21, 1893, and after qualifying at Guy's Hospital in 1918 went into general practice at Leyton, where he remained for a few years. About twenty years ago he moved to Portsmouth, where he became well known as a family doctor in the Fratton area. He lived for his work, and his death was a great loss to the district. Dr. Mullen was married, and the sympathy of his friends and patients will be extended to his widow.

Dr. JOHN FORBES died on July 8 at his home in central London. He was in his eighty-sixth year and until a few weeks before his death was still continuing a little private practice. John Forbes was the son of a general merchant at Muir of Ord, Ross-shire. He was a student at University College and at Edinburgh University, where he graduated M.B., C.M. in 1895. After being in practice in various parts of England and Scotland he eventually came to live in London, setting up practice in Shaftesbury Avenue in 1912. In due course he became an honorary physician to the Westminster General Dispensary, maintaining an interest in that institution until shortly before his death. He was also for many years public vaccinator for the area in which he lived. During the 1914–18 war he served for a period as a surgeon lieutenant and later as a major in the R.A.M.C. in the hospital ship *Dover Castle*. In 1940, despite his age, he was still very active in carrying on his practice, and visited nightly a number of air-raid shelters, including the tube shelters at Leicester Square and Covent Garden, thereby helping the authorities to achieve their task of preventing the spread of epidemics at that time. He joined the National Health Service for a few years, but retired when he was no longer able to give to the patients the care and attention which he thought they were entitled to expect. However, he continued in private practice and in particular was of great assistance to travellers who had to be vaccinated before going abroad. Popular with patients and colleagues alike, Dr. Forbes was a modest, friendly man, with one abiding interest outside his work. A Scot by birth, he felt that all Scots should do what they could to help their fellow countrymen in difficulties. He was a life governor of the Royal Scottish Corporation, which carries on a great and useful work in looking after aged Scots in London and elsewhere. A Gaelic scholar himself, he believed that Scots in London should be able to worship as they did in their parents' day, in Gaelic. He was a member for many years of the London Gaelic Services Committee, which holds quarterly services in the Gaelic language at Crown Court Church, near Bow Street. Dr. Forbes is survived by his widow and a son and a daughter, to all of whom our sympathy is extended. His elder son died during the war while serving as a surgeon lieutenant.

The death occurred on July 10, at his home in Bognor Regis, of Dr. FREDERIC LILLEY. He was 90 years of age. Born at Monkstown, County Antrim, he received his medical training in Dublin and Edinburgh, taking the Scottish triple qualification in 1897. After a period of assistantships, he began general practice in Selly Park and King's Norton, Birmingham, where in 1901 he married Mona Louise Williamson, of Scotstown, County Monaghan. Dr. Lilley was for many years a member of the urban district council of King's Norton and Northfield, being chairman of a number

of committees connected with health and education. He did much work for the St. John Ambulance Brigade, and was made an honorary life member. Retiring to Weston-super-Mare in 1922, he later recommenced practice on a small scale among his many Birmingham patients who had similarly retired to that area. His only son, Graham Lilley, died in 1932, a few years after qualifying as a dental surgeon. Soon afterwards Dr. and Mrs. Lilley moved to Bognor Regis to be with their married daughter. Mrs. Lilley died in 1949. Dr. Lilley was a younger brother of A. L. Lilley, Archdeacon of Ludlow and canon of Hereford Cathedral, and like him was a man of great intellectual capacity, with an alert mind active until the end. His kindness and old-world courtesy endeared him to all who knew him.

Dr. DOUGLAS D. C. THOMSON died at his home at Penrith, Cumberland, on July 12 at the age of 59. He practised in Penrith and the surrounding villages for thirty years until a failing heart forced his retirement about a year ago. Born at Bishop Yards, Penrith, on May 19, 1895, Douglas Durrand Christian Thomson was the fourth son of the late Dr. D. G. Pearce Thomson, who settled at Penrith in 1888. He was educated at Queen Elizabeth Grammar School, Penrith, at King William's College, Castletown, Isle of Man, and at the London Hospital. The first world war interrupted his medical studies and from the University of London O.T.C. he was commissioned in the Royal Garrison Artillery in 1916. He served on the Western Front at the battle of the Somme, at Vimy Ridge, and at Passchendaele, and was wounded at Ypres in 1917. On demobilization he returned to the London Hospital and qualified M.R.C.S., L.R.C.P. in 1922. After holding house appointments at "The London" until 1923 he returned to Penrith as assistant to his elder brother, Dr. J. R. K. Thomson, with whom he was later in partnership until 1950. He always gave unsparingly of his best, and earned an immense affection from all his patients, who knew him affectionately as "Dr. Doug." His death has brought to a close 66 years of medical practice in the district by the same family. Dr. Douglas Thomson was a great lover of antique furniture and silver, and in his retirement turned to gardening as a hobby so far as his health would allow. He was a vice-president of the British Legion and the Penrith Rugby Union Football Club, an honorary life member of the British Red Cross Society, Cumberland County Branch, and had been a master of the Ullswater Lodge of freemasons, honours of which he was very proud. In his medical student days he was vice-captain of the London Hospital Rugby fifteen and had also played tennis and golf. In 1925 he married Miss Dorothy Murray, who died in 1948, leaving two daughters. He married, secondly, Miss Elaine Hobart, who survives him, as do his elder brother, Dr. J. R. K. Thomson, and his sister, Miss Gyda Thomson.

The Services

A *Supplement* to the *London Gazette* has announced the following awards:

Second Clasp to the Territorial Efficiency Decoration.—Colonels M. De Lacey, O.B.E., T.D. (now A.E.R.), and D. H. Young, O.B.E., T.D. Majors L. P. Clarke, T.D., C. H. Imrie, T.D., and E. Shipman, T.D., R.A.M.C.

First Clasp to the Territorial Efficiency Decoration.—Colonel F. H. Blackburn, T.D., and Colonel M. De Lacey, O.B.E., T.D. (now A.E.R.). Lieutenant-Colonel I. C. A. D. P. Graham, T.D., and Majors R. W. W. Brown, L. P. Clarke, T.D., and M. H. Evans, M.B.E., R.A.M.C.

Territorial Efficiency Decoration.—Lieutenant-Colonels J. B. Heycock, M.C., H. A. Mullen, and T. P. Sewell, Major (Honorary Lieutenant-Colonels) M. S. Holman, Majors G. A. Bell, R. W. W. Brown, A. H. Emslie-Smith, M. H. Evans, M.B.E., J. G. A. Gilruth, F. W. Newby-Good, J. C. B. Serjeant, G. Swift, M. A. Watson, B. W. Wells, and Captain (Honorary Major) J. V. Wilson, R.A.M.C.

Medical Notes in Parliament

Legal Actions for Damages

Sir WALDRON SMITHERS (Orpington, Con.) on July 22 asked the Minister of Health how much money his department had paid in each year since the health services were nationalized in damages for neglect or inefficient medical or nursing treatment. Mr. IAIN MACLEOD stated that information in this precise form was not available, but he would circulate a table showing the total compensation payments of all kinds made by Health Service hospital authorities in England and Wales in each year to 1952–3, the latest year for which accounts were available. These payments very largely resulted from claims for damages in the kind of case Sir Waldron Smithers had in mind.

The statement gave the following figures:

	Amount £
July 5, 1948, to March 31, 1949	7,560
Year ended March 31, 1950	23,636
Year ended March 31, 1951	38,556
Year ended March 31, 1952	106,574
Year ended March 31, 1953	152,590

Sir WALDRON SMITHERS asked whether the Minister would ensure that the Press got the figures, which he would not willingly give in the House, and was this not further evidence that the Health Service under State control broke down when individuals were relieved of personal responsibility. Mr. MACLEOD: I resent and repudiate that question. I am publishing these figures at once, and the Press will have them at once. I am certain that there has been no deterioration of any sort in the care which is given since the Health Services were nationalized.

Mr. GEORGE THOMAS (Cardiff, West, Lab.) asked the Attorney-General whether he would appoint a medical man to serve on each local tribunal which decided whether to grant legal aid in cases where hospital authorities were being sued. Sir LIONEL HEALD replied, "No." Applications for legal aid to take proceedings against hospitals for negligence, he said, were in practice supported by medical opinions. The appointment of a medically qualified member would not enable the certifying committee to dispense with this evidence, and, as he would not have seen the applicant, he would not be able to add to it.

Hospital Staff Remuneration

Mrs. JEAN MANN (Coatbridge and Airdrie, Lab.) on July 22 asked the Minister of Health what assurances were given to hospital staffs, including senior hospital medical officers, registrars, etc., as to the acceptance of the Spens recommendations; how far he proposed to accept these recommendations; and what steps were being taken to implement the Spens Report as applicable to hospital staffs. Mr. IAIN MACLEOD replied that the recommendations in the Spens Report formed the basis for the terms and conditions of hospital medical staff which were agreed with the profession and published in 1949. He would like to make clear the Government's view that the remuneration of medical practitioners could not be settled by reference only to the recommendations of a report made six years ago, before any experience had been gained of the Health Service. As the Chancellor of the Exchequer said in the House on July 2, 1952, remuneration must be determined after taking into account all relevant circumstances. In the light of this, increased rates of pay had recently been introduced for hospital medical staff under an agreement with their representatives.

Over-prescribing Investigations

Mr. R. G. PAGE (Crosby, Con.) asked the Minister of Health on July 22 what was the administrative cost of investigations under Regulation 12(1) of Statutory Instrument, 1948, No. 507 (Investigation of Excessive Prescribing) during the past 12 months; and in how many instances, as a result

of such investigations, he referred a matter to a local medical committee. Miss PAT HORNSBY-SMITH, the Parliamentary Secretary, said that the administrative cost included some items which could not be exactly determined, but was estimated to be under £15,000 for the past 12 months; during that period eight cases were referred to local medical committees.

Mr. PAGE asked whether the Minister was satisfied that such elaborate investigations were producing worth-while results. Miss HORNSBY-SMITH said that there were two stages in the investigations. In the first instance the regional medical officer visited the doctor whose over-prescribing had been reported, and endeavoured to point out the effects of that over-prescribing and to obtain co-operation. In that respect 200 doctors had been interviewed, with an estimated saving of £300,000. It was only in extreme cases, in which a doctor refused to co-operate, that there was a reference to the committee, and that accounted for the low number of eight.

Mr. PAGE asked in how many instances during the past 12 months the Minister had directed executive councils to withhold money from a practitioner; what was the total sum so withheld; and what was the total of the excessive cost of prescriptions incurred in these instances. Miss HORNSBY-SMITH said the Minister directed the withholding of a total of £500 from three doctors in partnership. Independent referees estimated the excess cost of their prescribing to be £232 in a single month and remarked that they appeared to have been over-prescribing for a long time. Mr. PAGE asked whether the procedure had been examined in these cases, in which it often resulted that a doctor was fined only for a medical opinion which did not coincide with the majority medical opinion. Miss HORNSBY-SMITH said that she could not accept that. The committees were properly constituted under the Act, and the evidence was put to the Minister who came to such a decision only in grave cases.

Drugs for Private Patients

Mr. JOHN HALL (Wycombe, Con.) asked the Minister of Health on July 22 if, in view of the conflict of opinion between the British Medical Association and the Central Health Services Council's Committee on the question of the free issue of medicines and drugs to private patients, he would make a statement. Miss HORNSBY-SMITH replied that in the present situation the Minister would not feel justified in proposing any amendment of the Health Service Acts in this matter.

Mr. HALL asked if Miss Hornsby-Smith was aware that, apart from the B.M.A., the medical members of the committee which published the report had dissociated themselves from that part which denied to private patients the same right to receive medicines under the Health Service that was given to others. Was it not unjust that a citizen should be denied the right to use the service to which he had paid? Miss HORNSBY-SMITH said that Mr. Hall was misinformed. The report of the committee on General Practice was unanimous. Nineteen of the 23 members were medical practitioners and 11 were general medical practitioners. The particular difficulty in any suggestion of this kind was in trying to exercise any proper control over excessive prescribing if doctors were not also providing general medical services.

Psoriasis Treatment

Lieutenant-Colonel M. LIPTON (Brixton, Lab.) asked what arrangements were being made to improve hospital facilities for the treatment of out-patients suffering from psoriasis. Mr. IAIN MACLEOD stated on July 22 that facilities for the treatment of skin diseases, including psoriasis, had shared in the general improvement in out-patient services.

Dr. BARNET STROSS (Stoke-on-Trent, Central, Lab.) said that probably about half a million people were suffering from this condition. More money was needed for the provision of special baths and the kind of treatment needed. Would the Minister see that the regional hospital boards got this extra money when they asked for it? Mr. MACLEOD said he did not think it was a good system of allocating money that it should be done on regional board requests for a particular service.

Another "Mental Million"

Mr. K. ROBINSON (St. Pancras, North, Lab.) asked on July 22 if the Minister would repeat the special allocation of capital from central funds for mental and mental deficiency hospitals known as the "mental million," and if he would increase the amount substantially. Mr. IAIN MACLEOD stated that he intended that some special allocation should again be available next year for capital expenditure on these hospitals, but it would not be possible to increase the total allocation.

Reciprocal Health Service Arrangements

Sir GUY LLOYD (Renfrew, East, Con.) asked the Minister of Health on July 22 with what countries there were arrangements making medical assistance freely available to British nationals visiting them; and what efforts were being made to extend such arrangements to other countries, notably Canada. Mr. IAIN MACLEOD stated that full reciprocity with any other country was not at present practicable, since no other country provided for its own nationals a health service comparable with our own. The Brussels Treaty countries had a reciprocal agreement for giving medical assistance to indigent persons, and a Convention extending this arrangement to all members of the Council of Europe had recently been signed.

Sir GUY LLOYD asked the Home Secretary what instructions had been given to immigration officers about granting entry to persons whose sole purpose in travelling to this country was to attempt to get free medical or surgical treatment. Sir DAVID MAXWELL FYFE informed him that the general rule was that leave to land should be refused to an alien if the immigration officer was satisfied that the sole purpose of the alien's visit to the United Kingdom was to secure free medical treatment.

Cleaner Food Legislation

The Food and Drugs Amendment Bill was given a second reading by the House of Commons on July 23, after a debate in which its purposes were welcomed by all parties but in which there was sharp dispute on the extent to which these should be achieved by statutory requirement or advisory code.

Dr. CHARLES HILL, Parliamentary Secretary to the Ministry of Food, advanced four reasons for the preparation of the Bill. First, it was necessary to amend the 1938 Act because its rigidity limited the power to make regulations. Secondly, the development of food technology had produced the problem that it was difficult, and often impossible, to determine in advance what might be the long-term effect on health of the regular consumption of small quantities of the new chemicals added to food. Thirdly, food-poisoning was now almost wholly a matter of germ infection of food; it was preventable and need not happen. Fourthly was the desire to embody in permanent legislation some of the advances brought about under defence regulations.

The Bill brought up to date the regulations dealing with food composition, labelling, and advertising. The most important extension was the power to require the addition of substances to food—for example, vitamins to margarine. On the possibility of chronic toxicity, Clause 4 gave the new power to obtain information about the substances used; and armed with that, and possibly the results of research, too, the Minister would at least have greater knowledge to determine whether there was sufficient indication of possible harm to justify restriction or prohibition, without having to wait for proved damage to health.

The Bill did not require the registration of all premises—for example, catering premises and retail food shops—but it gave the power to do it. The penalty of £100 fine or three months' imprisonment had been made applicable to all offences. The real argument for registration was possibly to deter the persistent offender by the thought that he might

be put out of business by the withdrawal of registration. The Minister so far thought that such a sanction could be applied by the courts without registration.

Foods that were dangerous came almost entirely in two categories—meat or meat products that had been cooked and left exposed; and dairy foods, including cream. While it should not be suggested that the medical danger was wider than it really was, a much more fastidious approach to the danger of food infection was a necessary background. A large part of the solution of food-poisoning was educational, and the report of the Chief Medical Officer for 1952 suggested that the efforts had not been very successful so far. A great deal had been done, but there was a lag between the gaining of knowledge and its acceptance in terms of human conduct.

Dr. EDITH SUMMERSKILL, speaking for the Opposition, said the essence of the Bill—which was drafted almost entirely by the Labour Government—was the powers enabling the Minister to make regulations to protect the public. There had been shameful collusion and subservience by the Government to big business. The regulations had been drafted in accordance with the recommendations of the working parties on the catering trade and manufactured meat products, and the committee on meat inspection. They had been circulated to the catering interests, and the worst elements in the trade, supported by some Conservative M.P.s, had demanded that the proposals should be dropped or so modified as to be useless. The Minister had surrendered.

Dr. A. D. D. BROUGHTON (Batley and Morley, Lab.) said the education of food handlers in the simple principles of hygiene was more important than legislation. All the good that could be done by the use of elaborate and expensive equipment could be brought to naught by the dirty habits of one careless person. He recounted what had been done as a result of the course in hygienic food handling prepared by the St. John Ambulance Association, and their disappointment that the Minister had given little encouragement to their work.

Dr. BARNET STROSS (Stoke-on-Trent, Central, Lab.) said that 60% of food came from abroad, and there was no control of its treatment with chemicals while it was growing. He quoted with approval a statement in the Delaney Report: "No chemical should be permitted to enter the nation's food supply until its safety for use has been demonstrated beyond any reasonable doubt." The chemist could not be stopped entirely, but there should be some control over him. The provision for requiring information was an excellent step forward. What was needed was a body that would co-ordinate available information and research so that they could be put at the disposal of food manufacturers and chemists. There should be a sort of pharmacopoeia on the subject.

Dr. HILL, replying to the debate, described Dr. Summerskill's criticisms as misleading. On other points raised he said it would be senseless to include in regulations, and subject to heavy penalties, conditions the observance of which could not be secured in that way because they affected matters of common human conduct. Some of the provisions could be better provided for by by-laws.

Medico-Legal

RESPONDEAT SUPERIOR

IMPORTANT SCOTTISH DECISION

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

The first Division of the Court of Sessions in Edinburgh on July 21[1] took a long step forward towards the removal of the differences in the way in which the English and Scottish courts have treated the responsibility of hospital management boards for the negligence of their professional staff. The problem came before the court on reclaiming motions, the equivalent of interlocutory appeals in England, in two actions in which Lords Strachan and Guthrie had previously absolved the hospital authorities from vicarious responsibility. In both cases the first Division gave leave to appeal to the House of Lords.

The doctors against whom the negligence was alleged were in each case members of the permanent staff of the hospitals concerned. As Lord Cooper said in his judgment, they were whole-time salaried officers prohibited from private practice, normally resident on the hospital premises, and as such residents subject to a measure of disciplinary control. In the exercise of their professional judgment and skill they were subject only to the supervision and direction of the medical hierarchy under whom they were assigned duties.

The leading judgment was given by the Lord President, Lord Cooper, with whom Lord Carmont and Lord Russell concurred. He introduced his judgment by observing that the topic was one which had given rise to a long series of conflicting decisions in Scotland and England which had been subjected to powerful destructive criticism, and that the search for a constructive solution would doubtless end only in the House of Lords. There was no reason why the law of Scotland and the law of England should differ on this matter, and now that the hospitals of the United Kingdom were administered under a single scheme varying only in minor details on either side of the Border it was manifestly undesirable that different principles should apply according to the situation of the hospital in Scotland or England.

After a detailed survey of the decisions in Scotland and England, and after alluding to decisions in Canada, New Zealand, and the United States, Lord Cooper proceeded to pose the familiar questions. Were medical personnel for this purpose in a class apart from all other skilled persons? Was there a distinction between skilled persons who belong to a "profession" and those who do not? Was the problem whether the medical person was a servant of the hospital, and, if so, what is the true basis of the rule "respondeat superior"? Was there an implied contract by every patient not to hold the hospital responsible for negligence by its skilled staff? If so, how far did this depend on the hospital being a charitable institution?

Lord Cooper said that it was difficult to avoid the conclusion that the earlier decisions regarding voluntary hospitals were deeply influenced by the desire to protect charitable funds from claims for damages, though it was hard to see why a charitable hospital should be liable for negligence by its domestic though not by its medical staff.

In the present cases, however, the old point arose under new conditions with a new background. The court was concerned not with a voluntary hospital or other charitable organization, nor with a local authority hospital under the Public Health Acts, but with hospitals operating under the National Health Service. He could not read the statutory obligations of the hospital boards as involving no more than the introduction of the patient to the hospital medical staff but otherwise only "to provide an efficient, heated, clean, and wholesome sick-house . . . and to employ a competent staff." That might, as some judges had held on grounds which were nowhere vouched and had by no means commanded universal acceptance, have been the limited obligation of the old charitable hospital. Under the new Act and regulations the obligation on the State was in his view to treat the patient.

Lord Cooper said that he must regard doctors in the position of those concerned in the cases before the court as servants of the hospital boards for the purpose of the rule "respondeat superior," or at least as the agents to whom the boards had delegated the performance of the duties imposed on the boards by statute. Accordingly they were persons for whose negligence, if any, in the discharge of their professional work hospital boards must accept responsibility.

This decision brings the principle applied by the Scottish courts to doctors who are full-time employees into line with the English decisions. The Scottish courts may well in a

[1] *Scotsman*, July 22, 1954.

future case go on and adopt Lord Justice Denning's view that the same principle applies to the visiting consultant.

The Medical and Dental Defence Union of Scotland acted for the doctors. Solicitors: Messrs. Brown, Mair, Gemmill, and Hislop, and Messrs. Macpherson and Mackay.

SURGEON'S ENTERTAINMENT EXPENSES

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

The Chancery Division last week considered whether Mr. W. Gissane, surgeon-in-chief at Birmingham Accident Hospital, was entitled to claim income tax allowances for expenses incurred in entertaining distinguished visitors and in visiting other hospitals. Mr. Gissane had claimed tax relief in respect of £606 expenses. Out of this the General Commissioners of Income Tax had allowed £250 for car expenses, £100 for entertaining visitors, and £100 expenses incurred in visiting other hospitals. The Crown appealed against this. Sir Frank Soskice, Q.C., for the Crown, questioned whether the entertainment of distinguished visitors was part of the surgeon's duties.

Mr. Justice Roxburgh said that the £100 incurred in entertaining surgeons visiting the hospital from other countries had been found to be essential to Mr. Gissane in his role of surgeon-in-chief in entertaining such visitors. The visits to other hospitals were obviously of a professional character. It was clear that this was an abnormal case. He accepted the view that the hospital was a new type of emergency hospital. Mr. Gissane was said to be employed under the Terms and Conditions of Service of Hospital, Medical, and Dental Staff (England and Wales), but it was obvious that the schedule of duties applicable to a consultant surgeon at a particular hospital could not easily be applied to a consultant surgeon whose duty was to be on call to every hospital in the region. It was not surprising that these terms had little relevance in considering the duties of this particular surgeon. The Commissioners' findings in this matter were irreconcilable. He added that before one could ascertain whether the expenses were necessarily incurred by the surgeon in the performance of his duties they had to decide what the duties were. It would no doubt require some rather exceptional terms of employment to justify the expenses incurred in entertaining visitors. Perhaps the terms were exceptional.

His lordship said that on the material before him he could not reach any conclusion. It was his duty to refer the case back, and to leave it to the Commissioners to hear such further evidence as they thought proper in the circumstances.

Universities and Colleges

UNIVERSITY OF LONDON

The following candidates have been approved at the examination indicated:

THIRD M.B., B.S.—[1 6]June M. Cheetham, [1 3]R. D. Clements, [1 3]H. P. Cook, [1 4]I. C. Cree, [1 6]D. A. M. Ellis, [1 5]Marion C. Handscombe, [1 2]P. R. Holt, [1 4 6]D. E. Hyams, [1 6]Barbara M. Isles, [1 6]Wendy L. Jefferson, [1 4]J. J. Lewis, [1 5]J. C. A. Madgwick, [1 3 5]Margaret S. Meyer (University Medal), [1 2]O. Morton, [1 3 6]Celia M. Oakley, [1 5]P. J. Scheuer, [1 3]A. K. Thould, P. T. Abear, R. M. Adam, M. J. T. Adams, R. Agius, H. E. Aldridge, Patricia M. Alexander, Barbara A. M. Allen, L. N. Allen, Sheila Allison, J. B. Anderson, J. K. Anderson, Margaret G. Anderson, J. W. H. Andrews, R. H. D. Andrews, H. H. Annamanthodo, T. D. Annear, P. Apall-Olsen, B. M. Archer, A. P. Ardouin, Christine M. Armstrong, K. Ashcroft, P. J. Ashton, W. L. Ashton, Diana Austin, Margaret G. Bailey, C. R. W. Bain, A. S. Baker, P. L. R. Baker, Jacqueline E. Banbury, V. C. J. Barker, L. Barsey, V. H. Bartley, M. W. Beaver, D. G. Bennett, A. Berry, G. P. Billingham, E. D. Bird, J. Blagdon, A. S. Blake, Anthea Blofeld, W. W. Blue, A. P. Bolt, Gwyneth J. D. Botherway, W. N. F. Boughey H. Bourne, J. J. Bowen, A. Bradley, Evelyn L. F. Brazenor, R. A. Briggs, Elizabeth Britain, Angela I. Brooks, M. W. Brown, T. L. McK. Brown, J. A. A. Bullard, D. M. Burgess, J. C. Burt, P. F. Cameron, N. MacD. Campbell, Mary R. Capon, Jean Carberry, G. W. Carp, Patricia M. Carpenter, P. J. Carrdus, K. C. Carstairs, Mary E. Carter, G. V. P. Chamberlain, C. C. D. Chandler, Brenda A. P. Clark, R. M. Clark, B. M. G. Clarke, C. D. Collins, L. Collins, J. P. Colmer, R. C. R. Connor, T. P. Connor, R. Conroy, P. J. Constable, D. Constad, Wendy A. Cook, J. F. Copplestone, Olive M. Cory-Wright, W. R. Costain, A. G. Cox, V. E. Crapnell, Jean E. Cree, B. W. Cromie, M. R. Crompton, S. C. Cross, J. Curley, K. J. Dalgliesh, J. H. Darrell, J. L. Davies, J. R. E. Davies, M. K. Davis, R. N. Davis, R. E. Davis, W. A. Dawkins, B. Dawson, M. H. Day, Diana M. Dean, A. N. J. de Soysa, J. H. Dines, P. R. Donaldson, L. N. Dowle, Jean E. Drake, J. E. O. Dunwoody, R. J. Eagger, Evelyn J. Edgcumbe, R. W. Edmonds, Lise L. Einerl, K. B Ellington, Rosalind A. Elliott, R. A. Ellis, Carice Ellison, R. W. Emmerson, D. A. Evans, G. Evans, P. A. S. Evans, N. O. Eve, Rosemary B. Felton, P. Field, M. E. Fielding, K. J. I. Finlayson, Eve L. Fisch, P. J. Fitzpatrick, A. F. Floyd, R. D. Foord, P. I. Forbes, R. E. Forgie, Helen P. S. Foulds, A. S. E. Fowle, B. N. Foy, D. L. French, G. E. Fulford, A. T. R. Fuller, P. Garmon-Jones, E. B. Garner, R. A. Gawn, D. J. Gee, Grace M. Gee, E. R. Gibbons, A. W. Gilks, J. F. Gill, L. H. Glaser, N. Gold, H. Gordon, D. J. Gorham, A. C. Graham, A. I. Graham, R. A. Grande, Rosemary A. Grange, M. Grant, A. V. Grasset, B. P. Gregory, Eirwen Griffith, W. F. Griffith, E. A. Griffiths, H. C. Grocott, W. P. Hadlow, M. A. Hargreaves, F. A. S. Harris, Jean G. Harrison, Kathleen M. Harrison, Pamela M. Harrison, L. M. Hart, R. D'A. Harvey-Kelly, Elizabeth H. G. Haslam, M. J. Hawken, P. Hays, S. F. Hazelton, G. E. Hicks, J. P. Hicks, D. Hide, J. D. Hill, K. A. Hillard, P. Hinds, J. T. Hobbs, J. F. Hogben, F. A. Holden, G. M. R. Holliday, J. G Holt, D. P. Honey, P. E. Hoogewerf, D. J. Hudson, T. O. Hughes, J. G. P. Hunt, J. Iffland, Joan R. Inwald, A. D. Isaacs, D. C. Jackson, Marjorie D. Jackson, C. V. James, E. M. James, P. D. C. Jarman, J. G. Jeffreys, P. Jenkins, Bridget M. Johnson, F. C. Johnson, Richard D. Johnston, Robert D. Johnston, D. McK. Jones, F. W. Jones, H. D. Jones, I. H. Jones, T. Jones, J. A. Kay, G. B. Kelly, J. H. Kerridge, I. A. Key, D. W. S. Klee, J. M. Kneebone, P. F. Knight, P. N. Knight, K. K. Korsah, R. G. Lacey, Joan E. M. Lambert, C. E. Langham, N. A. G. Leadbeater, R. H. Lethbridge, Julie M. Levi, J. V. V. Lewis, R. J. R. Lewis, Patricia J. Lindhop, P. F. Lippold, A. F. M. Little, Antonia Lofts-Pierson, D. Longbourne, G. A. Low-Beer, R. J. Luck, W. S. Lund, P. R. Lyon, Irene M. McAndrew, H. R. B. McCauley, J. McIntosh, A. Mackay, J. H. K. Mackie, I. E. D. McLean, J. A. McMillan, E. L. McNeil, A. G. Malleson, Pauline A. Manfield, H. R. Marker, P. A. T. Martin, B. Martin-Smith, Shelagh Mathias, A. H. Maynard, J. D. Maynard, W. M. Mee, S. C. Melnick, Helen D. Meredith, H. C. Meredith, H. O. Middleton, Audrey Millar, M. G. Miller, K. F. Mole, A. A. D. Moore, K. A. M. Moore, W. G. Moore, B. R. Morgan, Janet E. Morgan, L. J. G. Morgan, Ruth Morlock, A. O. N. Morris, D. C. F. Muir, Sheela M. Mullally, A. W. Munks, D. D. Munro, J. S. Murrell, K. D. Neame, Grace E. Nicholls, Elizabeth M. Nicholson, T. W. Nicholson, Wendy E. Noble, Joan H. Nuttall, Janet F. Nye, B. O'Connor, Margaret M. R. O'Garra, H. W. L. Oliver, A. T. Otaki, J. G. Owen, L. W. Padgett, Mary G. Paine, Patricia Painter, E. G. Palmer, D. C. Panday, R. Parkes, J. L. Pead, A. Pearce, J. F. Pearce, K. I. Pearce, A. J. Pearson, J. S. Peet, E. J. K. Penikett, Valerie J. Perkins, Margaret E. Pickering-Pick, D. H. Pickett, Diana J. Pippet, J. M. Pirrie, R. E. Piested, H. Poirier, B. J. Pollard, Mary D. Pollock, P. A. P. Pompa, C. W. Pook, B. J. Poole, A. M. W. Porter, M. W. Potts, J. K. Price, J. J. Prior, D. G. S. Randall, J. R. Rawstron, Dorothy S. Read, J. L. Read, A. L. A. Reid, Gwyneth M. Reiseger, J. E. S. Relton, T. M. Richards, Corinne J. Richardson, D. F. Rideout, Aileen B. Ridout, D. M. Roberts, D. Roberts, Anne E. Robinson, A. T. Robinson, J. F. Robinson, J. R. Robinson, P. Rodin, E. J. Roebuck, K. Ll. Rogers, W. F. Ross, Jill P. Rosser, H. E. Rowley, C. P. Royall, D. H. Rubens, Margaret Russell, Pamela D. Rustim, Joan M. Sadler, A. L. Sanderson, J. G. Sanderson, J. R. Scarr, D. G. Scott, Jane M. Scott-Brown, O. H. Shaheen, J. L. H. Sharp, L. Sharpe, Helen L. Shaw, A. M. R. Shirazi, J. C. Sibley, M. J. Smart, D. L. Smith, Enid P. Smith, Gillian M. W. Smith, J. C. Smith, R. H. Smith, R. W. Smith, D. L. Smithson, I. I. Snobar, Froma Somerville, J. G. Spink, Dorothy G. Stanley-Roose, D. Stansfield, F. L. D. Steel, A. Stenhouse, G. M. Stern, M. Stern, J. A. Stevens, J. H. Stevens, L. Stimmler, J. Stubbs, M. M. L. Sutcliffe, R. A. Sutherland, K. H. Sutton, Jane Sweatman, G. W. Tamlyn, T. H. Taylor, T. J. Taylor, H. A. J. Thomas, Eileen N. Thompson, D. Thorpe, E. E. D. Tomlin, K. H. Trigg, E. A. M. Tuck, Margaret J. Turpin, Annie M. N. Tustin, V. R. Twyman, G. H. A. Ullmann, J. F. Urquhart, H. L. D. Utidjian, Margaret M. Voysey, A. F. Wade, J. G. Wall, Alison S. Wallace, Betty Walmsley, D. A. Walmsley, F. W. Ward, A. A. Watson, R. W. Watton, D. A. D. Weir, J. A. Whitehead, H. W. Whitting, Dorothea M. Wigfield, Marian A. Wilkinson, D. H. Williams, A. J. P. Willis, J. H. P. Willis, A. H. Wilson, H. Wilson, A. J. Winterton, F. W. Winton, A. R. Wisdom, D. F. P. Wooding, Joan M. Woodley, D. Woodroffe, Celia B. M. Wookey, Enid M. Wozencroft, S. H. Wydell, B. A. Young, Sheila J. Young, C. F. A. Younger, C. L. Zoob.

[1]With honours. [2]Distinguished in pathology. [3]Distinguished in medicine. [4]Distinguished in applied pharmacology and therapeutics. [5]Distinguished in surgery. [6]Distinguished in obstetrics and gynaecology.

UNIVERSITY OF WALES

The following candidates at the Welsh National School of Medicine have satisfied the examiners at the examination indicated:

TUBERCULOUS DISEASES DIPLOMA.—W. G. L. Allan, S. Basuchaudhuri, J. L. Bhatia, L. H. Botha, S. Bovornkitti, C. G. I. Gordon, J. E. E. Henshaw, Nora M. A. Lehane, N. A. Nobbs, Kim Seng Oh, R. C. Ruiz, K. K. Sinha, R. Susai Mary, Hin Sun Wong.

QUEEN'S UNIVERSITY, BELFAST

The following candidates have been approved for the degree of M.D.: *By examination*, W. T. McClatchey. *By thesis*, F. Duff (with high commendation), W. T. E. McCaughey, R. G. S. Malone (with commendation), J. A. Weaver (with commendation).

The following candidates have been approved at the examination indicated:

FINAL M.B., B.CH., B.A.O.—*Part II*: J. P. Alexander, R. N. Armstrong, L. C. Banks, Margaret M. Beath, Elizabeth M. Beattie, E. P. Berwick, (with first-class honours), V. H. A. Black, D. S. Bolton, J. M. Bridges, F. R. B. Brown, Georgina D. Brown, Kathleen P. Browne, Margaret E. Burns, R. S. J. Clarke, J. H. Connolly, Aileen F. Connon, N. W. B. Craythorne, Florence M. Curran, Alice L. Davis, T. A. J. Dawson, J. C. Devlin, P. C. Elwood, N. D. Farnan, G. W. Fenton, J. J. Furlong, E. F. Glasgow, Helen M. Gorman, P. A. Gorman, A. Hamilton, H. D. Hayes, A. S. Hunter, Kathleen A. Irvine, Edna M. Irwin, B. F. Jamison, R. E. Kemp, B. S. L. Kidd, D. D. Kinn, S. J. Knox, Elizabeth P. Lees, Lavinia W. Loughbridge, J. H. Lowry, T. J. Lynch, H. A. Lyons, J. E. Lyttle, W. A. G. MacCallum, W. B. McConnell, Edith L. MacDermott, Rosemary H. McKinney, R. A. Mackintosh, D. F. McLaughlin, W. P.

McMillin, K. G. Maguire, Jay D. Mathers, R. E. Morrow, H. S. Nataros, W. J. Nicholson, Norah V. O'Neill, A. I. Y. Orr, P. R. B. Pedlow, J. H. Robertson, A. Roundhill, M. F. Russell, E. F. Sargaison, R. M. Shearer, June M. P. Shuttleworth, H. B. Stentiford, I. R. Wallace, J. Weatherup, S. M. Young.

UNIVERSITY OF BRISTOL

The dissertation submitted by N. C. Tanner, F.R.C.S., for the degree of M.D. has been approved.

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH

At a quarterly meeting of the College held on May 4, with the President, Professor L. S. P. Davidson, in the chair, the following were elected Members of the College: R. J. Peters, A. M. Fraser, I. Ahmad, T. P. Niyogi, A. J. Palwala, E. S. Shoucair, A. M. Jafar, K. Sengupta, R. Davies, J. L. Braudo, G. V. Feldman, A. Z. Abd-El Massieh, F. J. C. Perera, G. L. Walton, R. M. Foster, A. J. Williams, K. M. Win, S. Loganadan, R. G. Loudon, P. C. Bhalla, V. Ramadas, J. A. R. Lenman, B. S. Hartnett, D. W. Beaven, J. M. Reid, F. Starer, D. D. Pottinger, H. J. Woodliff, M. Braudo, L. J. P. Duncan.

At a meeting of the College held on May 26, with Mr. R. Leslie Stewart in the chair, the following candidates, having passed the requisite examinations, were admitted Fellows of the College: M. Y. Alyan, G. Choa, G. A. Clark, R. S. Cowie, J. A. Cunninghame, W. B. L. Downing, E. R. Duchesne, J. Fogel, P. J. F. Grant, M. E. Lake, T. G. Lorentz, J. B. Lowry, P. Madore, A. T. Matheson, V. S. Metgud, B. McL. More, P. O'Brien, A. F. Rateb, A. N. Razdan, I. Robins, M. Salvaris, R. T. Singh, C. D. Sinha, J. A. van der Merwe, R. I. H. Welsh.

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

At a meeting of the College held on June 4, with the President, Dr. Edward T. Freeman, in the chair, the following Members were admitted to the Fellowship: A. P. Grant, R. St. J. Lyburn (*in absentia*).

The following successful candidates at the recent examination were admitted to the Membership:

H. T. F. Barniville, Mary E. Bewley, F. R. Counihan, C. K. Heffernan, F. Hillman, M. J. Lalor, A. J. MacDonald, H. McVey, S. Miller, W. A. Norris, A. P. H. Randle, C. Reid, D. S. Wilson.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

The following candidates have been awarded the Diploma in Obstetrics:

Pauline A. Adams, D. A. Aiken, D. J. M. Allan, N. J. W. Allan, G. A. Ames, W. M. Anderson, Liselotte Asch, S. Bajpai, G. S. Banwell, D. W. Barnes, Rosalind A. Barnes, Margaret N. Barr, Mary M. Baxter, Jean M. Beecroft, Elspeth V. Beveridge, J. C. H. Bird, W. P. Black, A. S. Blake, R. Blight, M. L. Bloom, F. P. Brown, J. W. Browning, Hilda M. Brunt, Marjory M. Buchanan, A. M. Burnford, Nancy I. Cardno, Kim Choy Chong, Marjorie Coates, A. Cohen, T. I. Cope, C. E. Cosgrove, Mary G. Coyle, Audrey N. Crocker, K. A. Dalal, C. Dansie, A. Davies, Jean M. Davies, J. I. W. Davies, Joan V. Davis, G. B. Davison, V. E. Dean, J. Y. N. Devine, J. J. Devine, R. D. P. Druitt, B. Dudley, D. Duffin, J. Dunlop, C. P. E. Elliott-Binns, J. J. Enright, D. L. Evans, Mary E. Ll. Evans, Jeanette G. Eveson, M. A. Fenton, Isabella C. Ferguson, J. Fine, Alison M. M. Fleming, Margaret B. Fox, Mary U. Franklen-Evans, J. A. Girling, I. Goldman, J. H. Goode, P. M. Goodrich, P. D. Grant, Elizabeth D. Grassie, Hilary A. Hagan, Elizabeth M. Haines, C. J. J. Herlihy, K. M. Hewitt, Frances M. Hill, Sheila H. Hoey, Catharine E. Hollman, J. M. H. Hopper, J. Houston, E. Howarth, T. M. Howell, D. C. Hudson, Doreen R. Hyder, Sylvia R. Ingold, H. Jackson, R. F. Jackson, Lelia Jennings, I. M. Johnstone, K. Kanagsingam, D. P. J. Kelleher, E. I. Kohorn, K. T. Koussa, S. R. S. Laing, J. S. P. Lane, June P. Lawson, W. R. Lee, P. A. Lowe, Gwladys N. McCoach, J. Q. McCubbin, Jill MacDonald, Margaret R. MacD. McGilvary, Catriona D. McLeod, R. N. Malins, C. F. R. Mallett, G. C. Mansfield, J. Manuel, Patricia L. Martin, C. J. G. Menzies, Barbara I. Miller, J. S. M. Mitchelson, I. A. Moollan, Donalda M. Morgan, Mavis H. Mortimer, A. L. I. Murphy, R. N. Nag, T. M. O'Brien, J. F. O'Kelly, E. G. Old, Chiew Seng Oon, Elspeth M. Orr, Margaret O'Sullivan, D. N. H. Owen, N. S. Painter, C. E. Parr, K. C. Parsons, Dinah Patuck, H. J. B. Pershad, W. Peter, C. D. Peters, P. B. Poole, Sylvia E. Prebble, J. F. Preece, W. E. B. Preston, D. S. Ractliffe, T. F. Regan, Jean E. Ritchie, Kathleen M. Robb, T. E. Roberts, K. F. Robinson, Patricia M. Russell, I. Sahney, J. F. Scarlett, R. Schofield, A. Schutz, F. G. M. Seager, Janet Shaw, R. G. Sinclair, G. D. Smellie, Janet U. A. Smith, S. A. Smith, Carol M. S. Spence, T. J. Stanton, Mary J. Starbuck, J. K. Steel, M. Steele, D. H. Stewart, I. A. Stewart, W. M. B. Strangeways, Mary W. Sturges, J. S. V. Surman, Muriel M. H. Sutcliffe, W. R. Swaffield, G. S. Tapsall, M. K. Thompson, N. A. Toes, Dorothy I. Troup, A. G. Turner, S. Vakil, M. H. Vickery, J. de M. Vink, P. O. Wakelin, Phyllis M. Wallington, D. G. Walker, A. G. Wallace, I. H. Watson, Josephine P. Werren, Susanne M. Williams, A. C. Wilson, D. G. Wilson, G. C. Winch, Hazel G. Wiseman, K. A. Wood, D. W. B. Woolven, E. G. B. Worthington, A. P. Wright, M. A. Young.

ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATION

The following candidates were successful at the Association's May examination for the Diploma in Psychological Medicine:

D.P.M.—*Part I*: P. Baker, I. A. Cameron, A. Capstick, H. W. Conran, D. C. W. Jenkins, P. K. Ray, L. F. W. Rowe, R. V. Shirvaikar. *Part II*: J. K. Arkle, U. B. H. Baruch, N. C. Connell, T. B. Stephens, R. M. Taylor.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **July 10** (No. 27) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	19	3	2	0	2	25	1	10	1	
Dysentery	711	115	148	6	1	557	79	171	2	1
Encephalitis, acute	7	0	0	0		9	1	0	0	
Enteric fever:										
Typhoid	3	0	0	1	0	0	0	1	0	
Paratyphoid	5	0	0	0	0	23	1	2(B)	0	
Food-poisoning	405	14		1	0	998	16		1	
Infective enteritis or diarrhoea under 2 years				11	17				8	24
Measles*	2,690	121	74	191	223	7,580	291	371	233	210
Meningococcal infection	14	0	15	0	1	27	2	21	1	
Ophthalmia neonatorum	21	3	8	0		37	3	12	1	
Pneumonia†	248	12	102	0		370	12	159	6	
Poliomyelitis, acute:										
Paralytic	46	4	12	0	0	44	3	4	5	2
Non-paralytic	19	2				21	1			
Puerperal fever§	237	43	5	1	0	261	35	15	2	
Scarlet fever	807	56	111	29	35	1,223	92	193	37	64
Tuberculosis:										
Respiratory	749	99	150	25				164	30	
Non-respiratory	119	9	22	2				40	5	
Whooping-cough	2,085	98	171	23	90	4,104	344	530	61	113

DEATHS in Great Towns	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0		0
Dysentery	1	0		0		1	1			
Encephalitis, acute		0			0		0			
Enteric fever	0	0	0	0		0	0	0		
Infective enteritis or diarrhoea under 2 years	7	2	0	0	2	6	0	0	0	1
Influenza	0	0	0	1	0	8	0	0	0	0
Measles		0	0	0	0		0	0		0
Meningococcal infection		0	0				0	0		
Pneumonia	130	19	11	12	4	148	20	19	6	4
Poliomyelitis, acute	2	0			0	2	0			1
Scarlet fever		0	0	0	0		0	0		0
Tuberculosis:										
Respiratory	80	12	10	1	4	73	11	7	3	8
Non-respiratory		3	12	0	3		0	3	1	0
Whooping-cough	0	0	0	0	0	4	0	0	0	0
Deaths 0–1 year	208	28	29	9	13	212	17	27	9	14
Deaths (excluding stillbirths)	4,543	632	305	108	142	4,447	596	529	92	127
LIVE BIRTHS	7,628	1166	921	204	452	8,026	1236	937	230	362
STILLBIRTHS	181	21	31			221	29	19		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

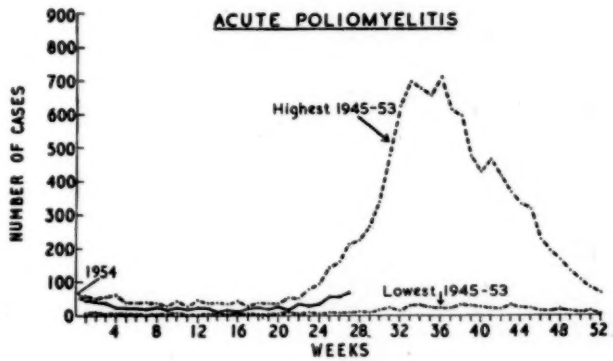
England and Wales—June Quarter

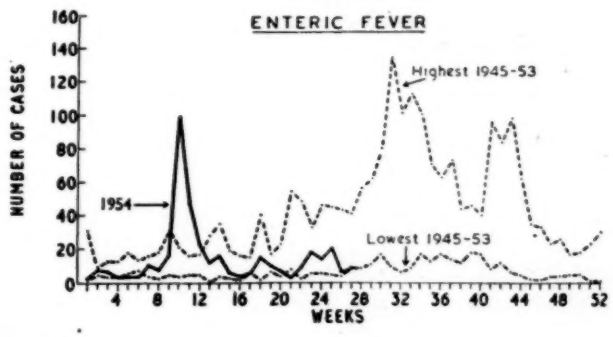
Live births registered numbered 175,467, giving a rate of 16.0 per 1,000 population.[1] Comparable rates for the second quarters of 1953 and 1952 were 16.4 and 15.9. There were 117,233 deaths registered, giving a rate of 10.7 per 1,000 population, compared with a rate of 10.5 in the second quarter of 1953 and 10.6 in the second quarter of 1952.

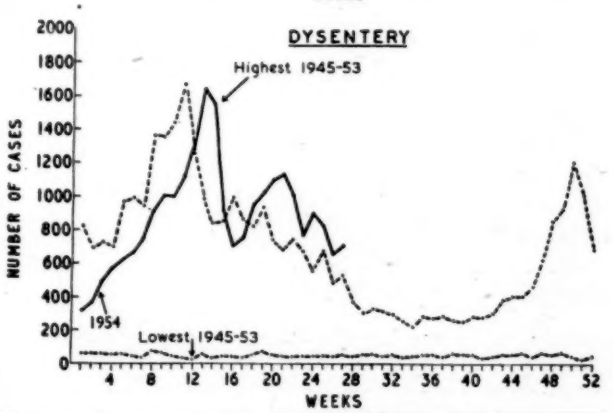
Deaths of children under 1 year of age numbered 4,262, giving a record low rate for a June quarter of 24.7 per 1,000 related live births, compared with a rate of 25.6 in the corresponding quarter of 1953 and 50.3 in 1938. There were 4,153 stillbirths registered, giving a rate of 23.1 per 1,000 total live and stillbirths, compared with a rate of 22.9 in the corresponding quarter of 1953.

Graphs of Infectious Diseases

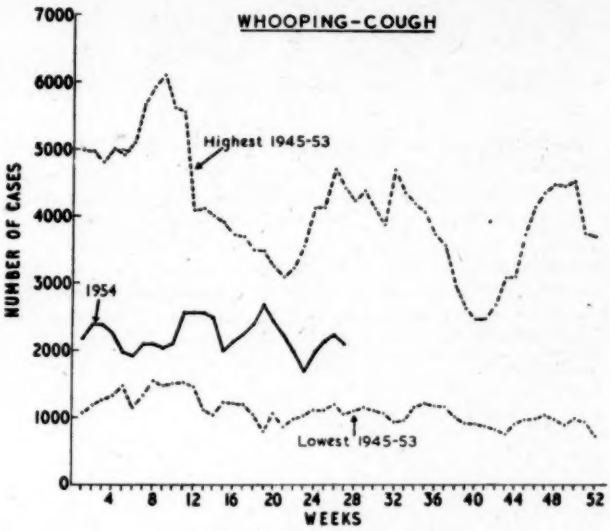
The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1945–53 are shown thus - - - - - -, the figures for 1954 thus ————. Except for the curves showing notifications in 1954, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







[1] *Registrar-General's Weekly Return*, No. 28, 1954.



Infectious Diseases

The chief fluctuations in the trends of infectious diseases in England and Wales during the week ending July 10 were decreases of 395 for measles, from 3,085 to 2,690, and 126 for whooping-cough, from 2,211 to 2,085, and increases of 66 for scarlet fever, from 741 to 807, and 50 for dysentery, from 661 to 711.

The largest decreases in the local trends of measles were 80 in Yorkshire North Riding, from 236 to 156, 57 in Durham, from 328 to 271, 56 in Staffordshire, from 156 to 100, 47 in Norfolk, from 176 to 129, and 46 in Cumberland, from 135 to 89, and the only large exception to the decreasing trend was a rise of 88 in Lancashire, from 540 to 628. The largest variations in the returns for whooping-cough were increases of 44 in Durham, from 70 to 114, and 43 in Derbyshire, from 34 to 77, and decreases of 53 in Warwickshire, from 158 to 105, and 36 in Surrey, from 88 to 52. 19 cases of diphtheria, 1 fewer than in the preceding week, were notified. The chief features of the returns for diphtheria were an increase from 0 to 3 in London and from 4 to 7 in Lancashire. Only small variations were recorded in the local trends of scarlet fever.

65 cases of acute poliomyelitis were notified during the week. These were 11 more for paralytic and the same for non-paralytic as in the preceding week. The largest returns were Yorkshire East Riding 11 (Kingston-upon-Hull C.B. 8, Haltemprice U.D. 2), Northumberland 7 (Newcastle-upon-Tyne C.B. 6), London 6 (Camberwell 2), Cheshire 6 (Birkenhead C.B. 2, Wallasey C.B. 2), and Durham 6 (Sunderland C.B. 3, Easington R.D. 2).

The chief centres of dysentery were Lancashire 149 (Stretford M.B. 45, Manchester C.B. 18, Liverpool C.B. 12, Haydock U.D. 11), London 115 (Fulham 51, Lewisham 13), Yorkshire West Riding 92 (Sheffield C.B. 44, Rotherham R.D. 17, Leeds C.B. 11), Leicestershire 50 (Leicester C.B. 44), Worcestershire 31 (Oldbury M.B. 26), Warwickshire 28 (Birmingham C.B. 22), Kent 27 (Penge U.D. 18), Lincolnshire 26 (Boston M.B. 15), Middlesex 24, and Northumberland 21.

235 of the 405 cases of food-poisoning were notified in Kent (Rochester M.B. 131, Chatham M.B. 99).

Week Ending July 17

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 802, whooping-cough 2,235, diphtheria 11, measles 3,073, acute pneumonia 312, acute poliomyelitis 63, dysentery 608, paratyphoid fever 13, and typhoid fever 11.

Increased Lung Cancer in Liverpool

The number of deaths from cancer of the lung in Liverpool rose from 160 in 1945 to 432 in 1953. This "startling increase," as Professor A. B. Semple, M.O.H. for Liverpool, describes it, is recorded in his report for 1953.

Medical News

Cortisone and A.C.T.H.—The Ministry of Health has increased the number of hospitals issuing cortisone and A.C.T.H. to 144. Larger supplies of cortisone are available for ordinary use, and also preparations for use at special sites, such as a suspension of hydrocortisone acetate for intra-articular injection, cortisone acetate eye ointment, and hydrocortisone acetate skin ointment. The issuing hospitals have complete discretion in the selection of patients for treatment with their ordinary supplies of cortisone and A.C.T.H., but in certain conditions where maintenance treatment is regarded as essential to life the Ministry will provide extra supplies. These conditions are adrenal deficiency (including Addison's disease and the post-adrenalectomy state), pituitary deficiency (including Simmonds's disease, Sheehan's syndrome, etc.), disseminated lupus erythematosus, polyarteritis nodosa, pemphigus, exfoliative dermatitis, sarcoidosis, congenital adrenal hyperplasia (pseudohermaphroditism), acquired haemolytic anaemia, and thrombocytopenic purpura. In England and Wales all applications for cortisone and A.C.T.H., whether for N.H.S. or private patients, must be made to one of the issuing hospitals, whose names are available at regional board offices. In Scotland there are five distribution centres: the Eastern Regional Hospital Board; Raigmore Hospital, Inverness; the Royal Infirmary, Aberdeen; the Royal Infirmary, Edinburgh; and Stobhill Hospital, Glasgow.

Honorary Fellows of the R.S.M.—On July 20 Sir WILLIAM GILLIATT, the President of the Royal Society of Medicine, conferred honorary Fellowships on Sir ALEXANDER FLEMING, F.R.S., Professor JOHN FULTON (Harvard), Mr. V. E. NEGUS, and, *in absentia*, Professor G. M. FASIANI (Milan), Sir HOWARD FLOREY, F.R.S., and Dr. ALBERT SCHWEITZER (Nobel Laureate for Peace, 1952).

Hospital Diets.—King Edward's Hospital Fund for London has issued a new "guide to the cost of feeding patients, with menus and recipes," entitled *General Hospital Diets*. It contains 36 weekly menus that are nutritionally balanced and have been costed at the average wholesale and retail prices prevailing in 1953; it is intended to bring the pricing up to date annually. The book also contains 700 recipes on which the menus have been based. The menus are meant primarily for patients on general diet, and, since conditions vary so widely between hospitals, they have been planned in three grades. The top grade costs 27s. a week wholesale, the middle 25s., and the lowest 22s. All the menus provide an adequate diet from the nutritional point of view. The book can be bought for 3s. 6d. (post free) from the Fund's Offices at 10, Old Jewry, London, E.C.2.

St. Mungo Chair of Pathology, Glasgow.—Dr. THOMAS SYMINGTON, senior lecturer in pathology at the Glasgow Royal Infirmary, has been appointed to the St. Mungo (Notman) Chair of Pathology at Glasgow. He is 39. Dr. Symington was educated at Cumnock Academy and Glasgow University, where he graduated B.Sc. with honours in biochemistry in 1936, M.B., Ch.B. in 1941, and M.D. with honours in 1950. He became A.R.I.C. in 1952. In 1944 he was appointed an assistant and in 1947 a lecturer in the pathology department at the Glasgow Royal Infirmary. He served for two years in Malaya during the emergency. Dr. Symington has recently been awarded a travel scholarship by the Royal Infirmary so that he may visit this summer centres in Canada and the United States where research on the adrenals is being done.

International Union of the Medical Press.—The International Union of the Medical Press (Union Internationale de la Presse Médicale), which was established at a meeting in Brussels last year, held its first congress in Turin during the International Medico-Surgical Assembly which met in that city last month. Representatives from Belgium, France, Germany, England, Greece, Italy, Portugal, Spain, and Switzerland attended the congress, which was held under the joint presidency of Professor T. OLIARO, of Turin, and Professor M. LOEPER, the president of the Union. Among the subjects discussed were the place of films and microfilms in the diffusion of medical knowledge, the use of medical journals as instruments for ascertaining medical opinion, abstracts of medical articles, and the presentation of medical information in the general press. After some discussion the congress passed a resolution urging that contact be established between the national associations of the medical press and the editors of newspapers, and recommending that each paper should have a medical adviser with whom the lay journalists could discuss the problems relating to the publication of medical news. After a meeting of the general assembly of the International Union of the Medical Press, at which Paris was chosen as the meeting-place for the next congress, Professor T. Oliaro welcomed the delegates at a banquet in the magnificent new offices of Minerva Medica, the well-known Italian publishing house.

International College of Surgeons.—At a meeting of this College on September 9 this year in Chicago a "Hall of Fame" is being dedicated to the memory of the world's notable contributors to surgery, and a room of this hall has been set aside for Britain. Dr. J. F. BRAILSFORD, 20, Highfield Road, Edgbaston, Birmingham, 15, who is treasurer and secretary of the College for Britain, is anxious to have material for this hall to honour the memory of British surgeons. Any surgeon wishing to attend the meeting in September is invited to communicate with Dr. Brailsford.

Royal College of Obstetricians and Gynaecologists.—QUEEN ELIZABETH THE QUEEN MOTHER has sent a donation to the Silver Jubilee Building Appeal Fund.

Institute of Diseases of the Chest.—Clinical demonstrations on various aspects of chest disease will be given on Fridays at 5 p.m. in the lecture-room of the Institute (in the grounds of the Brompton Hospital, Fulham Road, S.W.3). These demonstrations are intended for candidates for higher qualifications. They are open, without fee, to medical practitioners on signing the attendance book. The first series will begin on October 1 and end on December 17.

"Giornale Italiano di Chemioterapia" is a new quarterly journal published by the Italian Society of Chemotherapy, 20, Via Darwin, Milan, at an annual subscription of 6,000 lire. The first number contains 48 papers on experimental and clinical aspects of chemotherapeutic agents.

Royal Sanitary Institute.—In recognition of their work for public health Dr. J. J. O'DWYER, principal medical officer of Unilever Bros., and Dr. C. G. PAYTON, M.O.H. of Northampton, have been awarded the Fellowship of the Royal Sanitary Institute.

Welsh Honorary Degrees.—Honorary degrees of the University of Wales were conferred on Sir HENRY COHEN and Dr. ERNEST JONES at the University College of Swansea on July 20. Sir Henry Cohen received an honorary LL.D. and Dr. Jones an honorary D.Sc.

Professor W. D. Newcomb has been given the title of Professor Emeritus of Morbid Anatomy on his retirement from the chair of morbid anatomy at St. Mary's Hospital Medical School.

Dr. R. G. White, Freedom Research Fellow at the London Hospital, has been appointed to the university readership in bacteriology tenable at the London Hospital Medical College.

Dr. J. H. Wilkinson, Ph.D., senior lecturer in chemical pathology at Westminster Medical School, has been appointed to the University readership in chemical pathology tenable at the School.

B.M.A. Library.—The Library will be closed and the library service suspended until August 16 while redecorating is being done.

COMING EVENTS

Conference on Treatment of Cerebral Palsy.—At B.M.A. House, London, September 28–30, under the presidency of Professor N. B. CAPON. Speakers from U.S.A. and Britain. Details from Secretary, British Council for the Welfare of Spastics, 13, Suffolk Street, London, S.W.1. (Amended notice.)

APPOINTMENTS

DANBY, THOMAS ANYAN, M.B., Ch.B., D.P.H., Consultant Psychiatrist, and to act as Deputy Physician-Superintendent, Leybourne Grange Colony, South-East Metropolitan Regional Hospital Board.

HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London, W.C.—N. R. Butler, M.D., M.R.C.P., D.C.H., Medical Registrar and Pathologist; Elizabeth S. Barry, B.M., B.Ch., D.C.H., Part-time Registrar to the Department of Physical Medicine; June Stephenson, M.B., Ch.B., D.C.H., Assistant Resident Medical Officer, Tadworth Court; Gwendolyn R. Tapp, M.B., B.S., D.C.H., Resident Medical Officer, Tadworth Court; J. D. Aberdeen, M.B., B.S., B. Shandling, M.B., F.R.C.S., Norma A. Lloyd, M.B., B.Ch., House-Surgeons; Jean McI. Smellie, B.M., B.Ch., D.C.H., B. W. Webb M.D., M.R.C.P., D.C.H., L. Friedlander, M.B., B.Ch., M.R.C.P., D.C.H., J. R. Roberts, M.B., Ch.B., M.R.C.P., House-Physicians; Margaret Munro, M.B., Ch.B., M.R.C.P.Ed., D.C.H., House-Physician to the Neurological and Neurosurgical Unit.

LIVERPOOL REGIONAL HOSPITAL BOARD.—R. Pracy, M.B., B.S., F.R.C.S., Consultant Ear, Nose, and Throat Surgeon to Hospitals in the St. Helens, Warrington and Ormskirk Groups; E. M. Kupfer, M.B., B.S., F.R.C.S., Whole-time Assistant Orthopaedic Surgeon to the Chester Area; I. Ll. Francis, M.B., Ch.B., F.F.A. R.C.S., D.A., Part-time Consultant Anaesthetist to Hospitals in the Liverpool City Area; E. Glazowski, M.B., Ch.B., Whole-time Assistant Pathologist to Walton Hospital; P. F. O'Brien, M.B., B.Ch., D.P.M., Whole-time Assistant Psychiatrist to Winwick Hospital.

PHILLIPS, W. POWELL, O.B.E., M.R.C.S., L.R.C.P., D.P.H., Medical Officer of Health, City and Port of Cardiff, and Principal School Medical Officer.

SIDDLE, JOHN LANGLEY, M.B., B.S., D.P.H., Medical Officer of Health Urban and Rural Districts of Chester-le-Street and Assistant County Medical Officer, Durham County Council.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—F. T. Wheeldon, M.B., F.R.C.S., Consultant Orthopaedic Surgeon, Plymouth Clinical Area.

WOOLGROVE, CYRIL GEORGE, M.B., Ch.B., D.P.H., Medical Officer of Health, Shardlow Rural District Council and Long Eaton Urban District Council, Derbyshire.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Bryson.—On July 16, 1954, to Barbara (formerly Fiddian), M.B., Ch.B., wife of Bernard Bryson, a son—Mark Fiddian.

Crockett.—On July 22, 1954, at Brechin Place, London, S.W., to Joan, wife of Dr. G. S. Crockett, a daughter—Dora.

DEATHS

Beat.—On July 21, 1954, at the Princess Elizabeth Hospital, Guernsey, Channel Islands, John Reid Beat, M.D., of Collinghurst, Fort Road, St. Peter Port, Guernsey, aged 38.

Ciantar.—On July 21, 1954, Dominic Ciantar, L.R.C.P.&S.Ed., L.R.F.P.S., of Abercrave, Swansea.

Dawe.—On July 24, at Mount Vernon Hospital, Northwood, Middlesex, Charles Henry Dawe, M.R.C.S., L.R.C.P., D.P.H., Surgeon Captain, R.N., retired, of Benslow, Hitchin, Herts, aged 76.

Jackson.—On July 23, 1954, at Thetford, Norfolk, Charles Eric Sweeting Jackson, M.B., F.R.C.S., late of King's Lynn, Norfolk, and Churston Ferrers, South Devon, aged 66.

Knaggs.—On July 11, 1954, at University College Hospital, London, W.C., Henry Valentine Knaggs, M.R.C.S., L.R.C.P.

Letchworth.—On July 22, 1954, at St. Paul's Hospital, London, W.C., Thomas Wilfrid Letchworth, M.D., F.R.C.S., late of Harley Street, London, W., and Surbiton, Surrey.

Master.—On July 23, in a nursing home, Bristol, Alfred Edmund Master, M.B., B.Ch., Lieutenant-Colonel, R.A.M.C., retired, aged 85.

Molony.—On July 21, 1954, in Oxford, Lucy Selina Molony, M.B., B.S., formerly of Persia, and East Africa.

Wright.—On July 22, 1954, at The Cottage Hospital, Aldeburgh, Suffolk, Sydney Faulconer Wright, M.D., aged 88.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Myxomatosis

Q.—*What is the cause and method of spread of myxomatosis? Is there any risk of human infection?*

A.—Myxomatosis is caused by a filterable virus. The multiple lesions which are formed are rich in the infective agent. Transmission by direct contact can occur under both laboratory and natural conditions, but it is somewhat irregular if infected and normal animals are separated by a relatively short distance. The rapid spread of the disease under natural conditions is attributed to the activity of various species of mosquitoes and possibly other biting vectors which act as mechanical transmitters of the virus. Myxoma virus is very strongly species specific for the rabbit, and there is no evidence whatever that man is susceptible.

Vitamin B_{12} and Growth of Children

Q.—*Is vitamin B_{12}, or other preparation, of any value as a means of increasing the growth of a child otherwise normal?*

A.—First, it is important to be clear about what is meant by an "otherwise normal child." If this means a child in good general health, but small for its age, we may simply be dealing with a child of small or slow-growing stock. In that case we should leave well alone. On the other hand, if faulty nutrition is responsible for the failure to grow, then the diet should obviously be reviewed. So far as vitamin B_{12} is concerned, it is well established that this vitamin will often increase the rate of growth in normal pigs and poultry. The same effect is sometimes given by antibiotics, such as aureomycin, which probably exert their action by modifying the bacterial flora of the intestines. It seems possible that the action of vitamin B_{12} may also partly depend on its action in the intestines. There have been claims that the growth of undersized human children may be increased by vitamin B_{12}, but opinions are divided about its efficacy. Recently rather different claims, not specially related to undersized children, have been made by J. Yudkin for a special form of liver extract.[1] After being found valuable for the reproduction and growth of rats the extract was tested for about three months on groups of normal schoolchildren. Small additions in the increases in weight and height were recorded as compared with children in a control group. The growth-promoting factor was presumably not vitamin B_{12}. However, more substantial evidence of the reality of the increased growth, and of its significance, is needed before any final decision is reached on the value of this treatment.

REFERENCE

1 *British Medical Journal*, 1952, 1, 1388.

Hexachlorophene Soap

Q.—*What are the advantages of using soap containing hexachlorophene for "scrubbing-up"? Is there any danger of skin sensitization?*

A.—Hexachlorophene ("G11," 2,2'-dihydroxy-3,5,6,3',5',6'-hexachlorodiphenylmethane) is a powerful antiseptic with a remarkably persistent action. According to Cade[1] its regular use results after some days in a reduction of 90–98% in the numbers of bacteria recoverable from the skin of the hands; after its use is discontinued these numbers reach normal only when a week has elapsed. Fahlberg, Swan, and Seastone[2] found a 1% liquid soap containing it

more effective than a solid one; they also showed that hexachlorophene persists on the skin, whence it can be extracted with ether. It has not been reported to cause sensitization; Maglio and Hannegan[3] actually recommend its inclusion in skin-cleansing powders to prevent industrial dermatitis, although on somewhat hypothetical and perhaps insecure grounds.

All these observations refer to the normal "resident" flora of the skin, which is innocuous and impossible to eradicate completely. Whether the use of such soap will similarly suppress a "transient" flora which may include pathogens has not, so far as is known, been proved, although some such action seems likely. It may be assumed that there is some advantage in maintaining the hands in this condition, although this remains an assumption of which proof would be very difficult to obtain. It should be understood that constant use is necessary to achieve a sustained effect.

REFERENCES

[1] *Soap, N.Y.*, 1950, **26**, 35.
[2] *J. Bact.*, 1948, **56**, 323.
[3] *Soap, N.Y.*, 1952, **28**, 38.

Plastic Reconstruction of the Breast

Q.—*Is it possible to improve the bust of a flat-chested woman by plastic surgery? Neither pregnancy nor lactation produced much increase in the size of her breasts, and she is self-conscious about their smallness. Are there any contraindications to surgical treatment?*

A.—Flat-chestedness in women results either from failure of normal development of the breasts during adolescence, or from the effects of age, pregnancy, or lactation on small breasts. In the former case the breasts are normal in shape, contour, and firmness, but are diminutive. For these, if glandular treatment fails, surgery offers little. Attempts have been made to produce greater prominence by massive fat grafting in the retromammary space, but absorption is usual and the secondary defect unpleasant. In the latter variety, much can be done by plastic means to remodel the flabby collapsed tissues. The breast tissue and surrounding fat is reconstructed and supported by a tight skin brassière to produce a most satisfactory result. It is particularly in this type of collapsed breast that plastic surgery can be most helpful.

Hyperidrosis and Hexamethonium Compounds

Q.—*Are hexamethonium compounds of any value in the treatment of hyperidrosis? If so, what regime of treatment is recommended, and what are the contraindications and dangers?*

A.—The successful treatment of essential hyperidrosis, affecting principally the palms and soles, with hexamethonium bromide has been recorded by various authors. The drug has usually been given in the form of 250-mg. tablets, starting with one tablet three times a day and increasing to four or five times daily. The chief complications of treatment arise from other effects of the drug—namely, visual and salivary disturbances and fall of blood pressure. Owing to the latter it is usually considered advisable for patients to be taken into hospital or kept under very close observation in the early stages of treatment in order to determine a dose which will affect the hyperidrosis without producing serious side-effects. Unfortunately, this is not always possible, so that the side-effects may be worse than the original disorder.

The results of treatment are variable. Some authors claim excellent results and have found that patients do not relapse even after the drug is stopped. Sometimes the drug seems to fail to stop sweating, and in yet other cases tolerance seems to be established and patients relapse even while dosage is continued. Although this method of treatment for hyperidrosis is not particularly satisfactory, it would certainly seem best to try this before resorting to sympathectomy.

NOTES AND COMMENTS

Inheritance of Congenital Deafness.—Dr. L. FISCH (London, W.C.1) writes: In your issue of July 10 your expert was dealing in "Any Questions?" (p. 110) with the problem of the inheritance of congenital deafness. The derm "deaf-mutism" was used in the question and in the answer. I would like to take the opportunity to point out that this term is out of date, and objectionable for many reasons. First, it is objectionable to those who are born deaf but are able to communicate by speech adequately. Then it is objected to by those who are concerned with the education of the deaf because the term "deaf-mute" is an admission of failure in teaching the deaf to speak. Their argument is that it is not *their* failure but often that of those medical practitioners (including some otologists) who still give the advice to parents of deaf children to do nothing till the age of 5 (because they think nothing can be done), and then to send the children away to a residential school for the deaf. Medically the term implies that this type of deafness necessarily results in mutism, which is quite untrue. There are two types of hereditary congenital deafness. One is severe, with residual hearing in the lower range of frequencies only. The other one is moderate, with considerable hearing for all frequencies of sound used in speech. The severe-type children may have to be educated in deaf schools, but if adequate pre-nursery and nursery training is given, including auditory training as soon as the deafness is discovered, there is no need for them to become mute. The term "deaf-mute" reminds one of the term "deaf and dumb." This implied that the born-deaf was mentally deficient. We know now that the distribution of the various grades of innate mental abilities in the deaf population is not different from that in the general population. The term "deaf-mutism" should be abandoned altogether as medically incorrect, and the term "hereditary congenital deafness" should be used instead.

Intravenous Therapy in Infants.—Dr. LORNA G. MACDOUGALL (Nairobi) writes: With regard to the parenteral administration of fluids in infancy ("Any Questions?" May 15, p. 1166), I should like to comment on the use of intraperitoneal salines. Following the work of Dr. F. S. Carter[1] this method has been adopted in the children's wards of King George VI Hospital, Nairobi, with very satisfactory results. The technique is simple and involves the use of the standard giving set with a pint (570 ml.) of half normal saline and 2.5% glucose. The injection is made about one inch (2.5 cm.) above the umbilicus, in the midline, and the fluid (previousl wayrmed) allowed to run in a steady stream, the entire infusion of half to one pint being completed in 5 to 10 minutes. In the course of several hundreds of cases of dehydration treated in this manner there have been no fatalities directly attributable to this form of therapy, even in cases who have had repeated infusions. African staff have been instructed in this technique and can now carry out infusions without supervision. For further details as to technique I would refer your correspondent to Dr. Carter's original article, which is of great value to those dealing with dehydrated infants in the Tropics.

REFERENCE

[1] *E. Afr. med. J.*, 1953, **30**, 499.

Correction.—We regret that there was a printer's error in Miss Gladys M. Sandes's letter on "Treatment of Interstitial Keratitis" (July 24, p. 244). The full stop at the end of line 2 should be deleted, and line 3, "This is very rare, for, on careful inquiry, many admit that," should read, "treated with cortisone locally. We usually consider that."

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